PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 257/18, C07D 213/58, A61K 31/215, 31/44 — A1

(11) International Publication Number: **WO 99/00356**

(43) International Publication Date: 7 January 1999 (07.01.99)

(21) International Application Number: PCT/US98/13550

(22) International Filing Date: 26 June 1998 (26.06.98)

(30) Priority Data:
08/884,405 27 June 1997 (27.06.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 08/884,405 (CIP)
Filed on 27 June 1997 (27.06.97)

(71) Applicant *(for all designated States except US)*: RHÔNE-POULENC RORER PHARMACEUTICALS INC. [US/US]; Legal-Patents, Mail Drop #3C43, P.O. Box 5093, Collegeville, PA 19426-0997 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KLEIN, Scott, I. [US/US]; 27 Hampton Court, Norristown, PA 19402 (US). GUERTIN, Kevin, R. [CA/US]; 800 Kimberton Road, Phoenixville, PA 19460 (US). SPADA, Alfred, P. [US/US]; 473 Painter Way, Lansdale, PA 19446 (US). PAULS, Heinz, W. [CA/US]; 3770 Worthington Circle, Collegeville, PA 19426 (US). GONG, Yong [CN/US]; Apartment P61, 108 Eagle Stream Drive, Norristown, PA 19403 (US). MCGARRY, Daniel, G. [GB/US]; Apartment 148, 3000 Valley Forge Road, King of Prussia, PA 19406 (US).

(74) Agents: MARTIN, Michael, B. et al.; Rhône-Poulenc Rorer Pharmaceuticals Inc., Mail Drop #3C43, P.O. Box 5093, Collegeville, PA 19426-0997 (US).

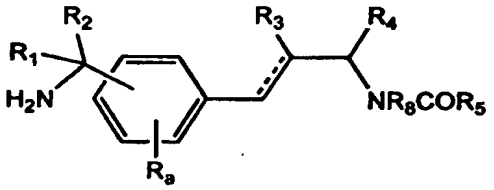
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SUBSTITUTED N-[(AMINOIMINOMETHYL OR AMINOMETHYL)PHENYL]PROPYL AMIDES

(57) Abstract

This invention relates to compounds of formula (I) which inhibit Factor Xa, to pharmaceutical compositions containing the compounds, and to the use of the compounds for the treatment of patients suffering from conditions which can be ameliorated by the administration of an inhibitor of Factor Xa.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

SUBSTITUTED N-[(AMINO)IMINOMETHYL OR AMINOMETHYL)PHENYL]PROPYL AMIDES

Field of the Invention

The compounds of formula I exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, they are Factor Xa inhibitors. The present invention is directed to compounds of formula I, compositions containing compounds of formula I, and their use, which are for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa.

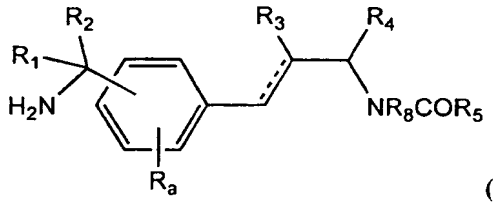
Factor Xa is the penultimate enzyme in the coagulation cascade. Both free factor Xa and factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula I. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy

is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

SUMMARY OF THE INVENTION

This invention is directed to a compound of formula I:



(I)

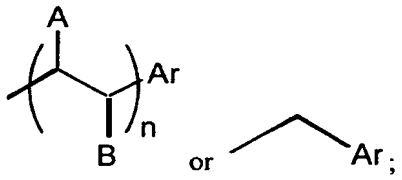
------ is a single or double bond;

R_a is hydrogen, hydroxy or amino:

R_1 and R_2 are hydrogen or taken together are $=NR_9$;

R_3 is hydrogen, $-CO_2R_6$, $-C(O)R_6$, $-CONR_6R_6$, $-CH_2OR_7$ or $-CH_2SR_7$;

R_4 is hydrogen, alkyl, Q-alkyl or thioheterocyclyl, or a group of formula



R5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, aryl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, heteroaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl, fused heterocyclylheteroaryl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, aralkynyl or heteroaralkynyl;

R_6 is hydrogen or lower alkyl;

R_7 is hydrogen, lower alkyl, Ar(lower alkyl), lower acyl, aroyl or heteroaroyl;

R_8 is hydrogen or lower alkyl;

R_9 is hydrogen, $R_{10}O_2C$-, $R_{10}O$-, HO-, cyano, $R_{10}CO$-, HCO-, lower alkyl, nitro, or $Y^{1a}Y^{2a}N$-;
R_{10} is alkyl, aralkyl, or heteroaralkyl;

Y^{1a} and Y^{2a} are independently hydrogen or alkyl;

A and B are hydrogen or taken together are a bond;

Q is R_7O- or R_7S- or Y^1Y^2N-;

Y^1 and Y^2 are independently hydrogen, alkyl, aryl, and aralkyl, or one of Y^1 and Y^2 is acyl or aroyl and the other of Y^1 and Y^2 is hydrogen, alkyl, aryl, and aralkyl;

Ar is aryl or heteroaryl; and

n is 0, 1 or 2; or

a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definitions

"Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 15 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 6 carbon atoms in the chain which may be straight or branched. The alkyl group may be substituted by one or more halo, cycloalkyl or

cycloalkenyl. Representative alkyl groups include methyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more halo. Representative alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. Representative alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl and decynyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 6 ring atoms. The cycloalkyl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative monocyclic cycloalkyl include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Representative multicyclic cycloalkyl include 1-decalin, norbornyl, adamantyl, and the like.

"Cycloalkenyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkylene rings contain about 5 to about 6 ring atoms. The cycloalkenyl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. A representative multicyclic cycloalkenyl is norbornylenyl.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system of about 3 to about ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before

heterocyclenyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Representative oxaheterocyclenyl groups include 3,4-dihydro-2*H*-pyran, dihydrofuranyl, fluorodihydrofuranyl, and the like. A representative multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Representative monocyclic thiaheterocyclenyl rings include dihydrothiophenyl, dihydrothiopyranyl, and the like

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heterocyclyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl is optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulphur atom of the heterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Aryl" means an aromatic monocyclic or multicyclic ring system of 6 to about 14 carbon atoms, preferably of about 6 to about 10 carbon atoms. The aryl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Representative aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" is optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before heteroaryl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. A nitrogen atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. Representative heteroaryls include pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl,

benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Fused arylcycloalkenyl" means a radical derived from a fused aryl and cycloalkenyl as defined herein by removal of hydrogen atom from the cycloalkenyl portion. Preferred fused arylcycloalkenyls are those wherein aryl is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. The fused arylcycloalkenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. Representative fused arylcycloalkenyl include 1,2-dihydronaphthylene, indene, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkenylaryl" means a radical derived from a fused arylcycloalkenyl as defined herein by removal of hydrogen atom from the aryl portion. Representative fused cycloalkenylaryl are as described herein for a fused arylcycloalkenyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused arylcycloalkyl" means a radical derived from a fused aryl and cycloalkyl as defined herein by removal of a hydrogen atom from the cycloalkyl portion. Preferred fused arylcycloalkyls are those wherein aryl is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. The fused arylcycloalkyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. Representative fused arylcycloalkyl includes 1,2,3,4-tetrahydronaphthyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkylaryl" means a radical derived from a fused arylcycloalkyl as defined herein by removal of a hydrogen atom from the aryl portion. Representative fused cycloalkylaryl are as described herein for a fused arylcycloalkyl radical, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused arylheterocyclenyl" means a radical derived from a fused aryl and heterocyclenyl as defined herein by removal of a hydrogen atom from the heterocyclenyl portion. Preferred fused arylheterocyclenyls are those wherein aryl is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl portion of the fused arylheterocyclenyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The fused arylheterocyclenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen or sulphur atom of the heterocyclenyl portion of the fused arylheterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused arylheterocyclenyl include 3H-indolinyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl,

1,2-dihydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused heterocyclenylaryl" means a radical derived from a fused arylheterocyclenyl as defined herein by removal of a hydrogen atom from the aryl portion. Representative fused heterocyclenylaryl are as defined herein for a fused arylheterocyclenyl radical, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused arylheterocyclyl" means a radical derived from a fused aryl and heterocyclyl as defined herein by removal of a hydrogen atom from the heterocyclyl portion. Preferred fused arylheterocyclyls are those wherein aryl is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heterocyclyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The fused arylheterocyclyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen or sulphur atom of the heterocyclyl portion of the fused arylheterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative preferred fused arylheterocyclyl ring systems include phthalimide, 1,4-benzodioxane, indolinyl, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 1H-2,3-dihydroisoindolyl, 2,3-dihydrobenz[f]isoindolyl, 1,2,3,4-tetrahydrobenz[g]isoquinolinyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused heterocyclylaryl" means a radical derived from a fused aryheterocyclyl as defined herein by removal of a hydrogen atom from the heterocyclyl portion. Representative preferred fused heterocyclylaryl ring systems are as described for fused arylheterocyclyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused heteroarylcycloalkenyl" means a radical derived from a fused heteroaryl and cycloalkenyl as defined herein by removal of a hydrogen atom from the cycloalkenyl portion. Preferred fused heteroarylcycloalkenyls are those wherein the heteroaryl and the cycloalkenyl each contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heteroaryl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The fused heteroarylcycloalkenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkenyl is optionally oxidized to the corresponding N-oxide. Representative fused heteroarylcycloalkenyl include 5,6-dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkenylheteroaryl" means a radical derived from a fused heteroarylcycloalkenyl as defined herein by removal of a hydrogen atom from the heteroaryl portion. Representative fused

cycloalkenylheteroaryl are as described herein for fused heteroaylcycloalkenyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused heteroarylcycloalkyl" means a radical derived from a fused heteroaryl and cycloalkyl as defined herein by removal of a hydrogen atom from the cycloalkyl portion. Preferred fused heteroarylcycloalkyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heteroaryl means that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylcycloalkyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl is optionally oxidized to the corresponding N-oxide. Representative fused heteroarylcycloalkyl include 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5-diazanaphthalen-2-onyl, 1,3-dihydroimidizole-[4,5]-pyridin-2-onyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused cycloalkylheteroaryl" means a radical derived from a fused heteroarylcycloalkyl as defined herein by removal of a hydrogen atom from the heteroaryl portion. Representative fused cycloalkylheteroaryl are as described herein for fused heteroarylcycloalkyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused heteroarylheterocyclenyl" means a radical derived from a fused heteroaryl and heterocyclenyl as defined herein by the removal of a hydrogen atom from the heterocyclenyl portion. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before heteroaryl or heterocyclenyl means that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylheterocyclenyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused heteroarylheterocyclenyl is optionally oxidized to the corresponding N-oxide. The nitrogen or sulphur atom of the heterocyclenyl portion of the fused heteroarylheterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused heteroarylheterocyclenyl include 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2-dihydro-1,6-naphthyridinyl, 1,2-dihydro-1,7-naphthyridinyl, 1,2-dihydro-1,8-naphthyridinyl, 1,2-dihydro-2,6-naphthyridinyl, and the like, in which the bond to the parent moiety is through a non aromatic carbon atom.

"Fused heterocyclenylheteroaryl" means a radical derived from a fused heteroarylheterocyclenyl as defined herein by the removal of a hydrogen atom from the heteroaryl portion. Representative fused heterocyclenylheteroaryl are as described herein for fused heteroarylheterocyclenyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Fused heteroarylheterocyclyl" means a radical derived from a fused heteroaryl and heterocyclyl as defined herein, by removal of a hydrogen atom from the heterocyclyl portion. Preferred fused heteroarylheterocyclyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclyl consists of about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The fused heteroarylheterocyclyl is optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined herein. The nitrogen atom of the heteroaryl portion of the fused heteroarylheterocyclyl is optionally oxidized to the corresponding N-oxide. The nitrogen or sulphur atom of the heterocyclyl portion of the fused heteroarylheterocyclyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Representative fused heteroarylheterocyclyl include 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2yl, 2,3,-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2 yl, 5,6,7,8-tetrahydro[1,7]napthyridinyl, 1,2,3,4-tetrhydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pryidyl, 3,4-dihydro-2H-1-oxa[4,6]diazanaphthalenyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro[5,8]diazanaphthalenyl, 1,2,3,4-tetrahydro[1,5] napthyridinyl, 1,2,3,4-tetrahydro[1,6]napthyridinyl, 1,2,3,4-tetrahydro[1,7]napthyridinyl, 1,2,3,4-tetrahydro[1,8]napthyridinyl, 1,2,3,4-tetrahydro[2,6]napthyridinyl, and the like, in which the bond to the parent moiety is through a non-aromatic carbon atom.

"Fused heterocyclylheteroaryl" means a radical derived from a fused heteroarylheterocyclyl as defined herein, by removal of a hydrogen atom from the heteroaryl portion. Representative fused heterocyclylheteroaryl are as described herein for fused heterarylheterocyclyl, except that the bond to the parent moiety is through an aromatic carbon atom.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls contain a lower alkyl moiety. Representative aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Preferred aralkenyls contain a lower alkenyl moiety. Representative aralkenyl groups include 2-phenethenyl and 2-naphthylethenyl.

"Aralkynyl" means an aryl-alkynyl- group in which the aryl and alkynyl are as previously described. Preferred aralkynyls contain a lower alkynyl moiety. Representative aralkynyl groups include phenacetylenyl and naphthylacetylenyl.

"Heteroaralkyl" means an heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl moiety. Representative aralkyl groups include pyridylmethyl, 2-(furan-3-yl)ethyl and quinolin-3-ylmethyl.

"Heteroaralkenyl" means an heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl moiety. Representative heteroaralkenyl groups include 2-(pyrid-3-yl)ethenyl and 2-(quinolin-3-yl)ethenyl.

"Heteroaralkynyl" means an heteroaryl-alkynyl- group in which the heteroaryl and alkynyl are as previously described. Preferred heteroaralkynyls contain a lower alkynyl moiety. Representative heteroaralkynyl groups include pyrid-3-ylacetylenyl and quinolin-3-ylacetylenyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Representative hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as previously described. Preferred acyls contain a lower alkyl. Representative acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" means an aryl-CO- group in which the aryl group is as previously described. Representative groups include benzoyl and
1- and 2-naphthoyl.

"Heteroaroyl" means a heteroaryl-CO- group in which the heteroaryl group is as previously described. Representative groups include nicotinoyl and pyrrol-2-ylcarbonyl and
1- and 2-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Representative alkoxy groups include methoxy, ethoxy,
n-propoxy, *i*-propoxy, *n*-butoxy and heptoxy.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Representative aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl groups is as previously described. Representative aralkyloxy groups include benzyloxy and
1- or 2-naphthalenemethoxy.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Representative alkylthio groups include methylthio, ethylthio, *i*-propylthio and heptylthio.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Representative arylthio groups include phenylthio and naphthylthio.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. A representative aralkylthio group is benzylthio.

"Y^1Y^2N-" means a substituted or unsubstituted amino group, wherein Y^1 and Y^2 are as previously described. Representative groups include amino (H_2N-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Representative alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Aryloxycarbonyl" means an aryl-O-CO- group. Representative aryloxycarbonyl groups include phenoxy- and naphthoxycarbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-CO- group. A representative aralkoxycarbonyl group is benzyloxycarbonyl.

"Y^1Y^2NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y^1 and Y^2 are as previously described. Representative groups are carbamoyl (H_2NCO-) and dimethylaminocarbamoyl (Me_2NCO-).

"$Y^1Y^2NSO_2$-" means a substituted or unsubstituted sulfamoyl group, wherein Y^1 and Y^2 are as previously described. Representative groups are sulfamoyl (H_2NSO_2-) and dimethylsulfamoyl (Me_2NSO_2-).

"Alkylsulfonyl" means an alkyl-SO_2- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl-SO- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Arylsulfonyl" means an aryl-SO_2- group.

"Arylsulfinyl" means an aryl-SO- group.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Ring system substituent" means a substituent attached which optionally replaces hydrogen on an aromatic or non-aromatic ring system. Ring system substituents are selected from the group consisting of aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano,

carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryldiazo, heteroaryldiazo, amidino, Y^1Y^2N-, Y^1Y^2N-alkyl-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, wherein Y^1 and Y^2 are independently hydrogen, alkyl, aryl, and aralkyl, or where the substituent is Y^1Y^2N- or Y^1Y^2N-alkyl- then one of Y^1 and Y^2 is acyl or aroyl and the other of Y^1 and Y^2 is hydrogen, alkyl, aryl, and aralkyl. When a ring system is saturated or partially saturated, the "ring system substituent" further comprises methylene (H_2C=), oxo (O=) and thioxo (S=).

acylamino, aroylamino,.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule(s) is/are H_2O.

"Prodrug" means a form of the compound of formula I suitable for administration to a patient without undue toxicity, irritation, allergic response, and the like, and effective for their intended use, including ketal, ester and zwitterionic forms. A prodrug is *trans*formed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

Preferred Embodiments

A preferred embodiment of the invention is a method for treating a disease state capable of being modulated by inhibiting production of Factor Xa to a patient suffering from said disease state an effective amount of the compound of formula I .

A preferred compound aspect of the invention is the compound of formula I wherein ------ is a single bond.

A preferred compound aspect of the invention is the compound of formula I wherein ------ is a double bond.

A preferred compound aspect of the invention is the compound of formula I wherein R_a is hydrogen.

A preferred compound aspect of the invention is the compound of formula I wherein

R_8 is hydroxy or amino; more preferred is hydroxy.

A preferred compound aspect of the invention is the compound of formula I wherein R_1 and R_2 taken together are $=NR_9$.

Another preferred compound aspect of the invention is the compound of formula I wherein R_1 and R_2 taken together are =NH.

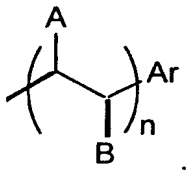
A preferred compound aspect of the invention is the compound of formula I wherein R_3 is hydrogen.

A preferred compound aspect of the invention is the compound of formula I wherein R_3 is $-CO_2R_6$, $-C(O)R_6$, $-CH_2OR_7$ or $-CH_2SR_7$; more preferred is $-CO_2R_6$, $-CH_2OR_7$ or $-CH_2SR_7$; yet more preferred is $-CO_2R_6$ or $-CH_2OR_7$.

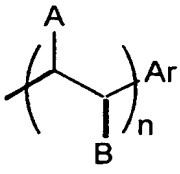
Another preferred compound aspect of the invention is the compound of formula I wherein R_3 is $-CO_2R_6$ and R_6 is lower alkyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_3 is $-CH_2OR_7$ or $-CH_2SR_7$ and R_7 is hydrogen or lower alkyl.

A preferred compound aspect of the invention is the compound of formula I wherein R_4 is hydrogen, alkyl or Q-alkyl, or a group of formula



Another preferred compound aspect of the invention is the compound of formula I wherein R_4 is lower alkyl or a group of formula



where A and B are hydrogen and n is 1.

A preferred compound aspect of the invention is the compound of formula I wherein R_4 is Q-alkyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_4 is R_7O(lower alkyl)-.

A preferred compound aspect of the invention is the compound of formula I wherein R_4 is thioheterocyclyl.

A preferred compound aspect of the invention is the compound of formula I wherein R_5 is alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused

heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl, fused heterocyclylheteroaryl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, aralkynyl or heteroaralkynyl; more preferred is fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl or fused heterocyclylheteroaryl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_5 is cycloalkyl, heterocyclyl, aralkyl or aralkynyl.

A preferred compound aspect of the invention is the compound of formula I wherein R_5 is aryl or heteroaryl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_5 is phenyl, naphthyl, or heteroaryl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_5 is phenyl substituted phenyl, heteroaryl substituted phenyl, phenyl substituted heteroaryl or optionally heteroaryl substituted heteroaryl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_6 is lower alkyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_7 is hydrogen or lower alkyl.

A preferred compound aspect of the invention is the compound of formula I wherein R_7 is Ar(lower alkyl) or heteroaroyl.

Another preferred compound aspect of the invention is the compound of formula I wherein R_8 is hydrogen.

Another preferred compound aspect of the invention is the compound of formula I wherein R_9 is hydrogen.

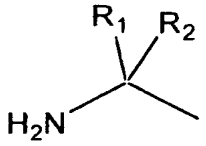
A preferred compound aspect of the invention is the compound of formula I wherein A, B, R_8 and R_9 are hydrogen.

Another preferred compound aspect of the invention is the compound of formula I wherein R_{10} is lower alkyl.

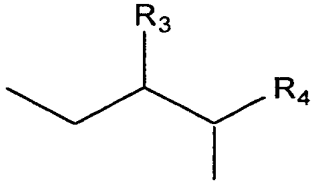
A preferred compound aspect of the invention is the compound of formula I wherein Q is R_7O-.

A preferred compound aspect of the invention is the compound of formula I wherein n is 1.

Another preferred compound aspect of the invention is the compound of formula I wherein the

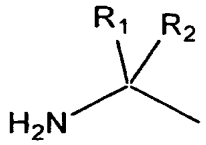


moiety is in the meta position to the position of attachment of the phenyl moiety to the

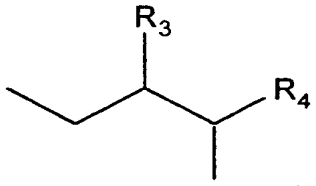


moiety.

Another preferred compound aspect of the invention is the compound of formula I wherein the



R_a is hydroxy or amino, more preferably hydroxy, which is in the para position to the H_2N moiety which is in the meta position to the position of attachment of the phenyl moiety to the



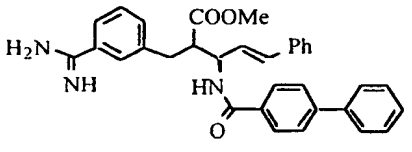
moiety.

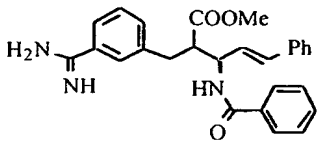
Another preferred compound aspect of the invention is the compound of formula I wherein Ar is aryl.

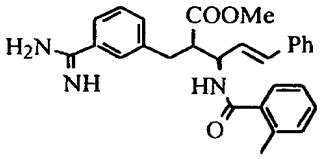
Another preferred compound aspect of the invention is the compound of formula I wherein Ar is phenyl.

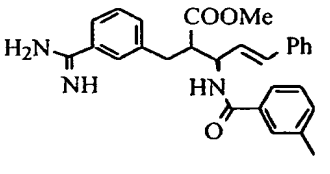
Included within the scope of formula I are compounds wherein R_1 and R_2 taken together are $=NR_9$, wherein R_9 is $R_{10}O_2C$-, $R_{10}O$-, cyano, $R_{10}CO$-, optionally substituted lower alkyl, nitro, or Y^1Y^2N-. Such derivatives may themselves comprise the biologically active compound useful for treating a disease state capable of being modulated by inhibiting production of Factor Xa to a patient suffering from said disease state, or may act as pro-drugs to such biologically active compounds which are formed therefrom under physiological conditions.

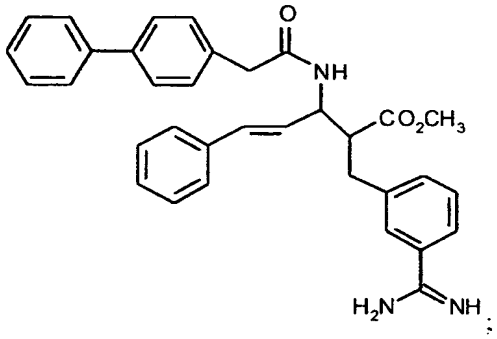
Species according to the invention are selected from the following:

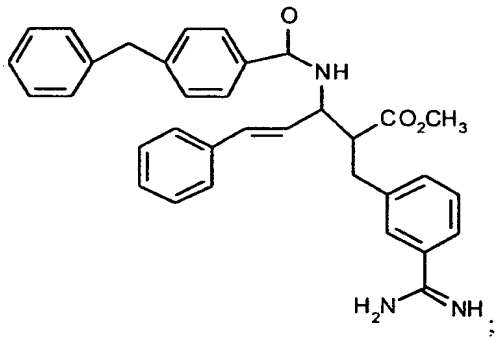

;

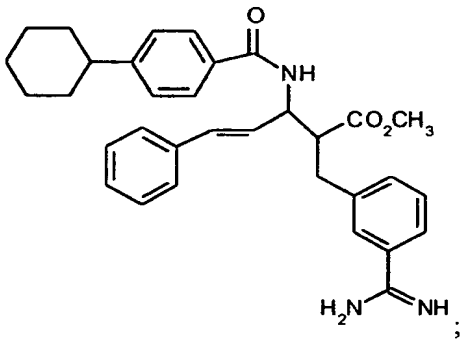

;

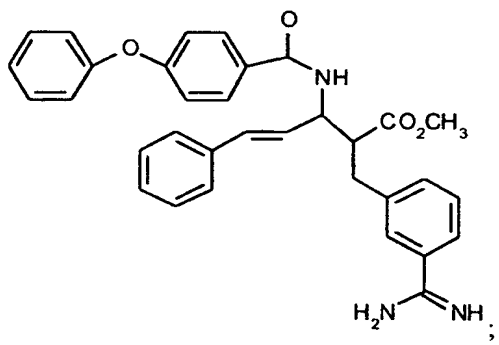

;

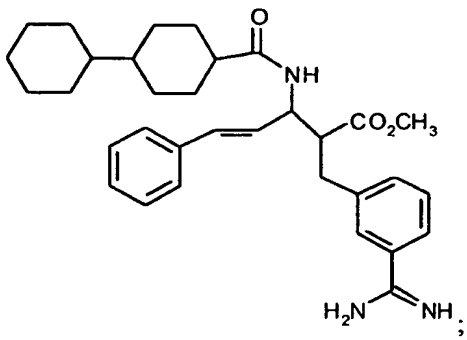

;

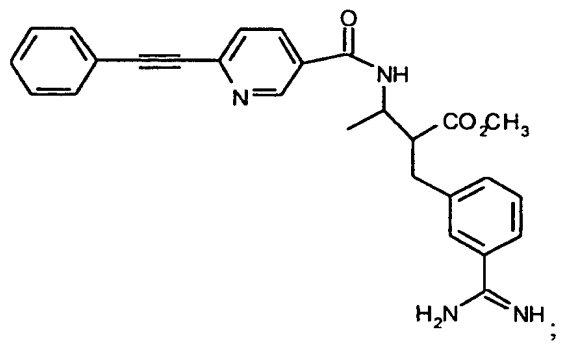

;

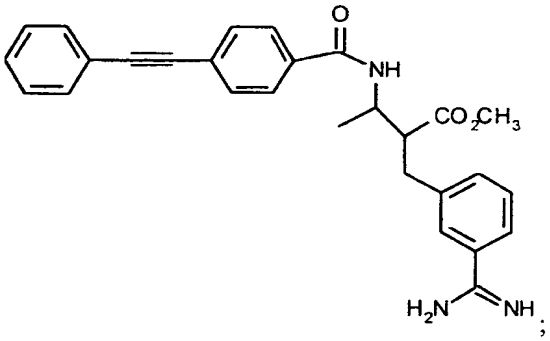

;

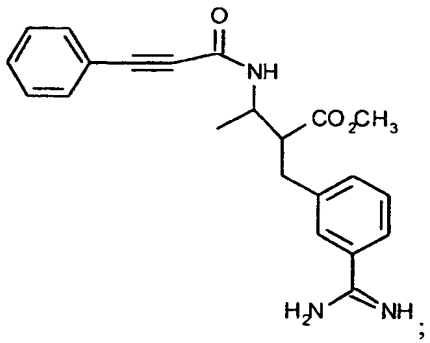

;

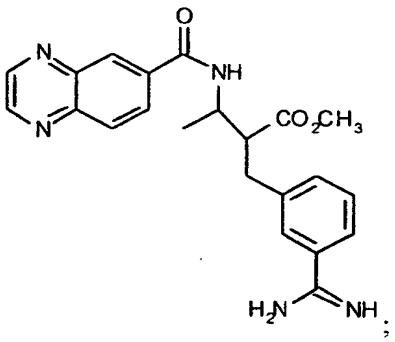

;

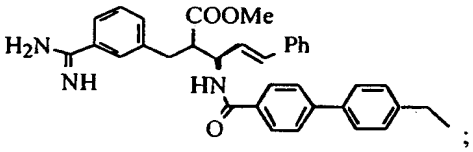

;

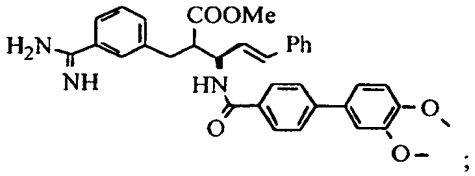

;

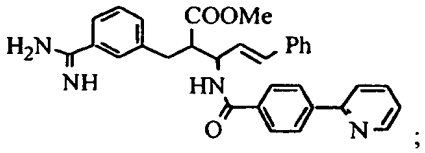


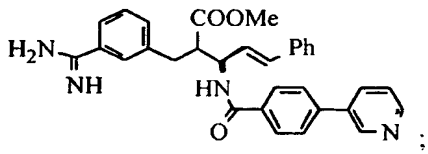


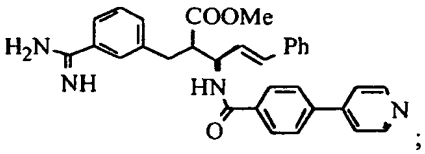


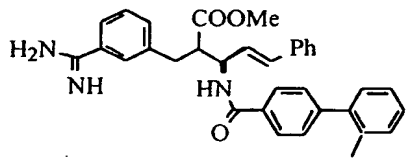


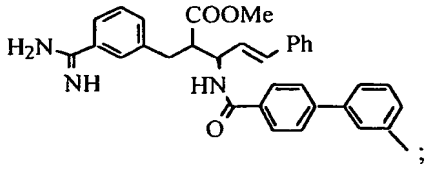


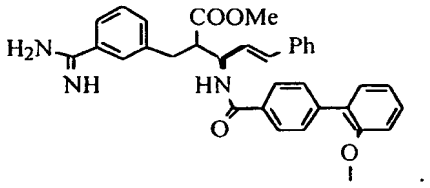


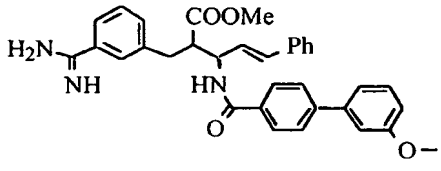


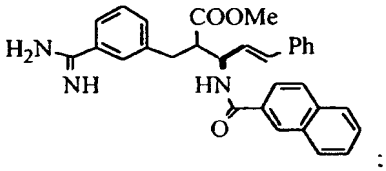


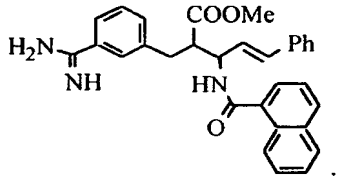


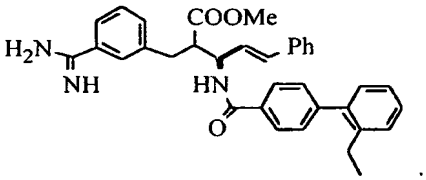

;

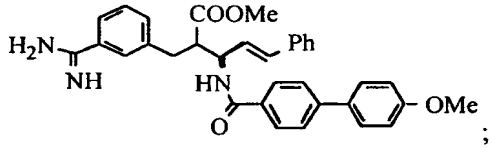

;

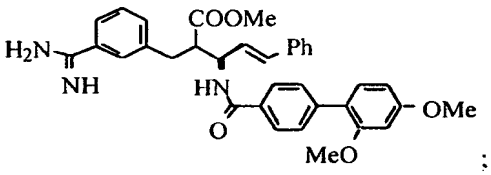

;

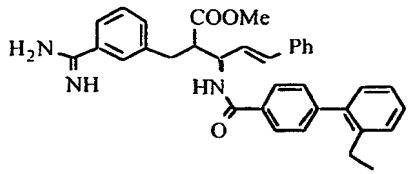

;

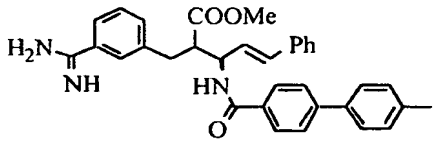

;

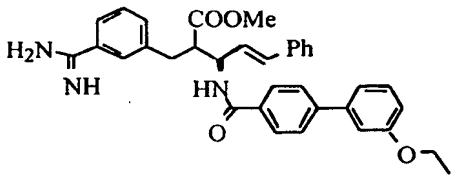

;

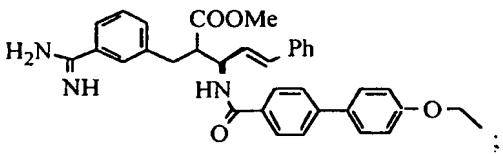

;

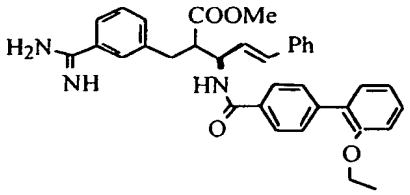

;

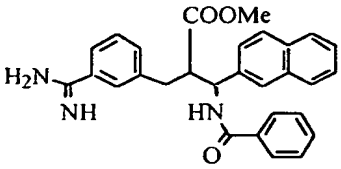

;

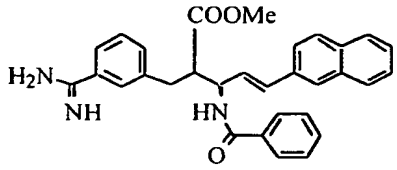

;

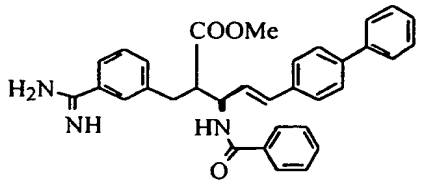

;

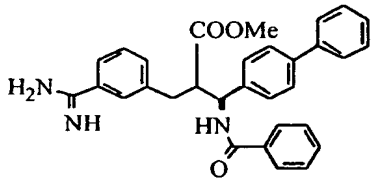

;

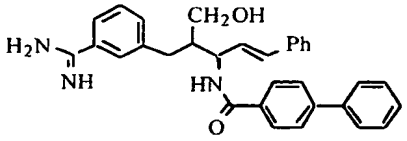

COOMe
Ph
H_2N
NH
HN
O
O
;

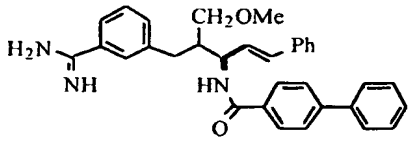

COOMe
H_2N
NH
HN
O
;

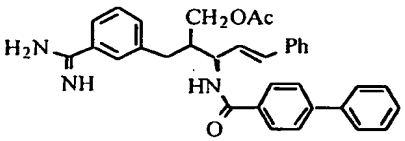

COOMe
H_2N
NH
HN
O
;

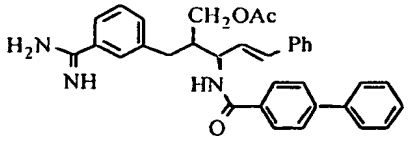

COOMe
H_2N
NH
HN
O
;

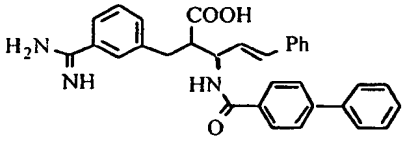

COOMe
H_2N
NH
HN
O
;

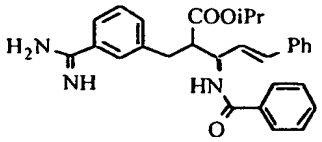

CH_2OH
Ph
H_2N
NH
HN
O
;

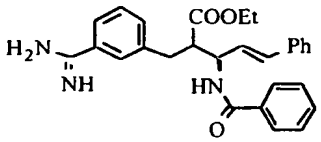

CH_2OMe
Ph
H_2N
NH
HN
O
;

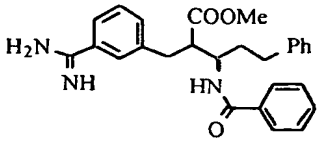

CH_2OAc
Ph
H_2N
NH
HN
O
;

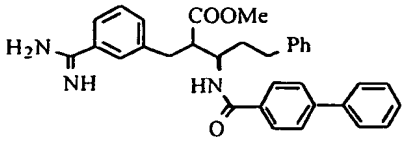

CH_2OAc
Ph
H_2N
NH
HN
O
;

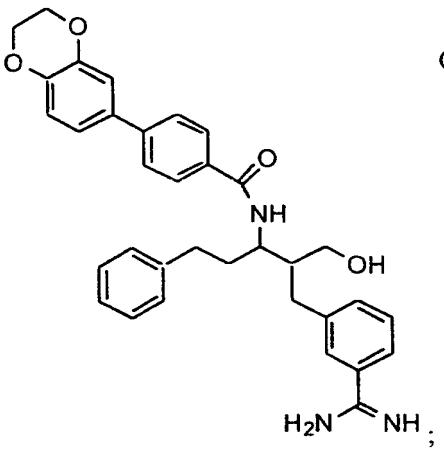

COOH
Ph
H_2N
NH
HN
O
;

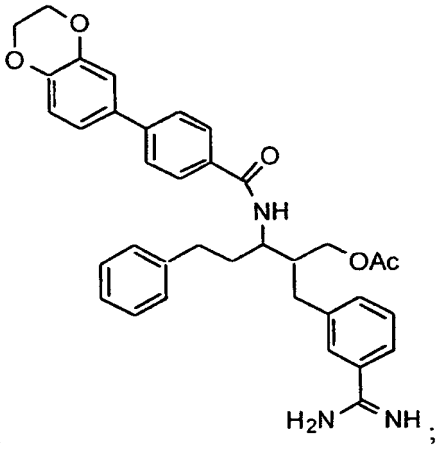

COOiPr
Ph
H_2N
NH
HN
O
;

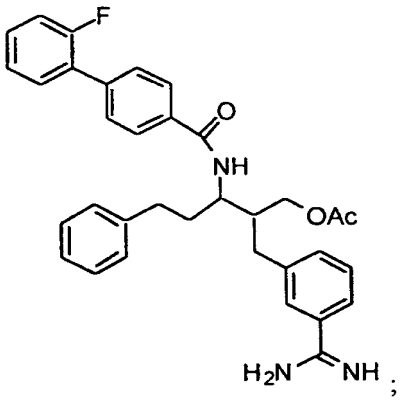

COOEt
Ph
H_2N
NH
HN
O
;

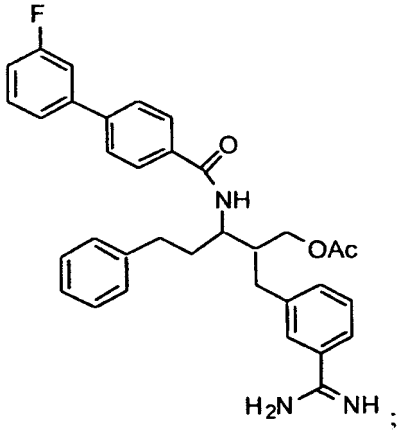

COOMe
Ph
H_2N
NH
HN
O
;

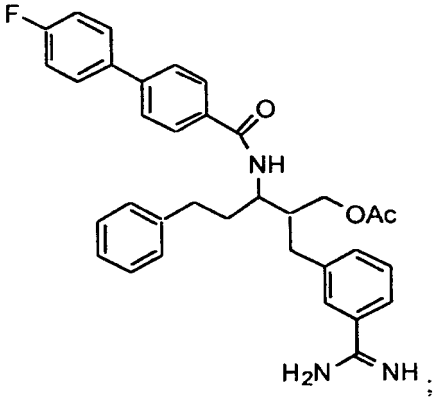

COOMe
Ph
H_2N
NH
HN
O
;

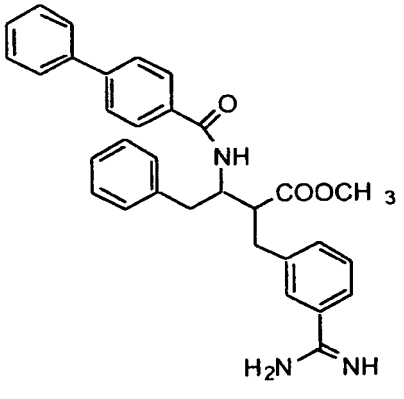




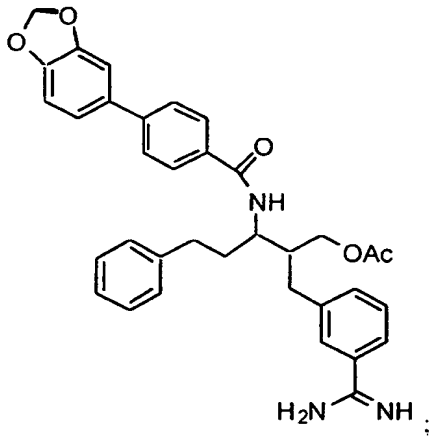


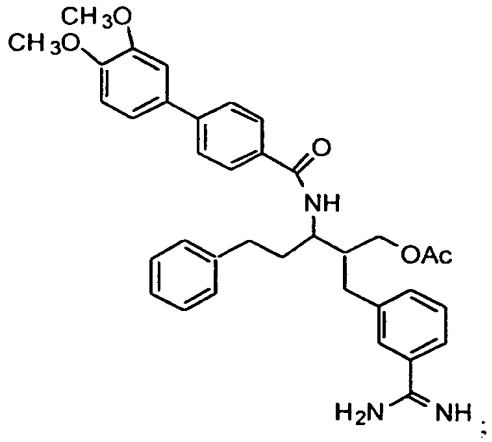


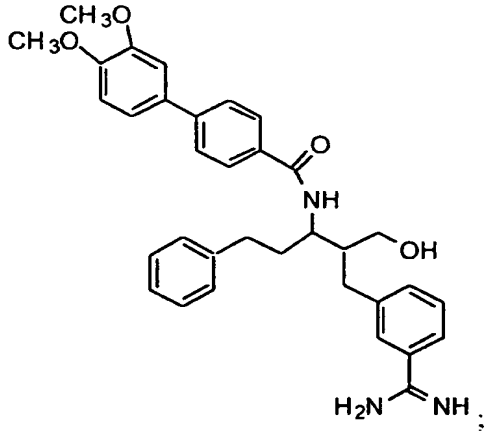


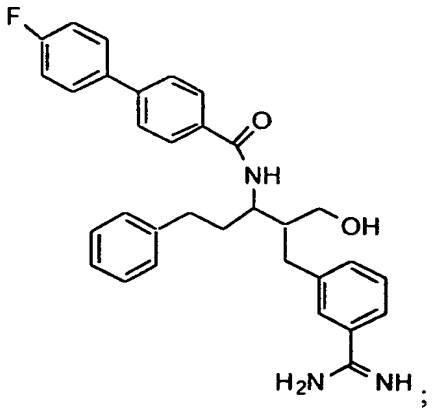


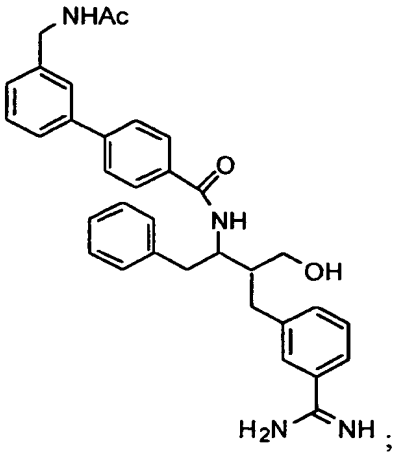
5

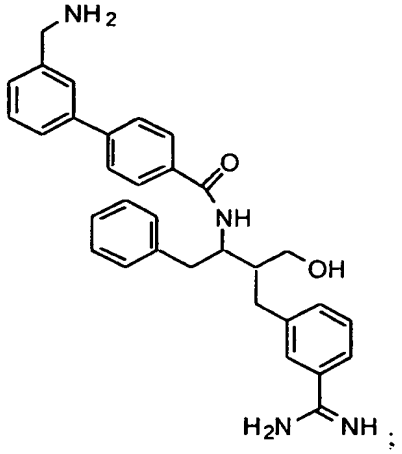




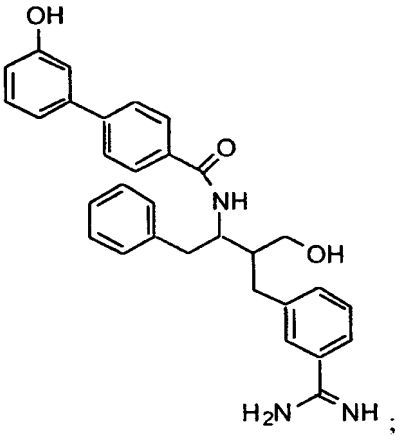


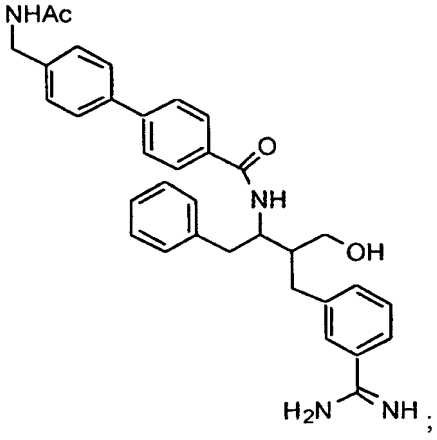


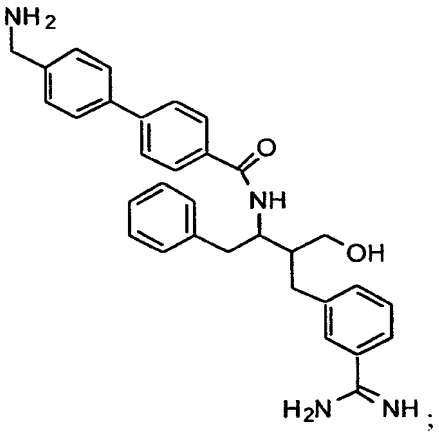


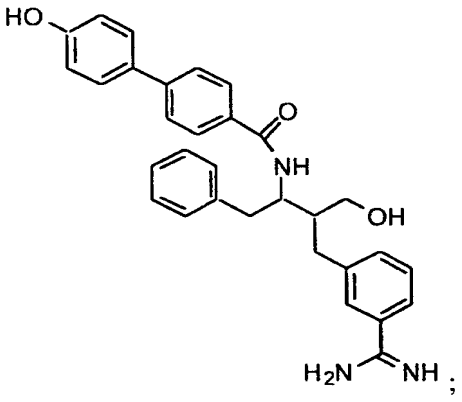


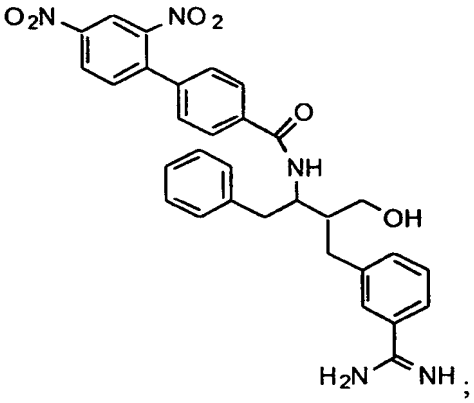
5

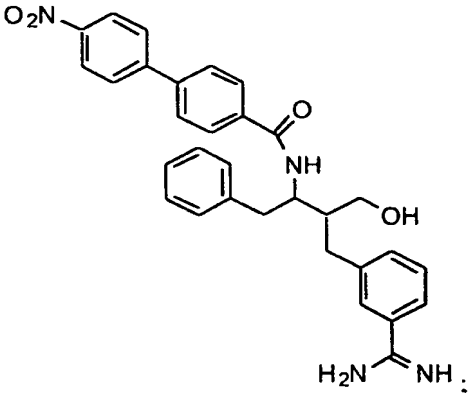




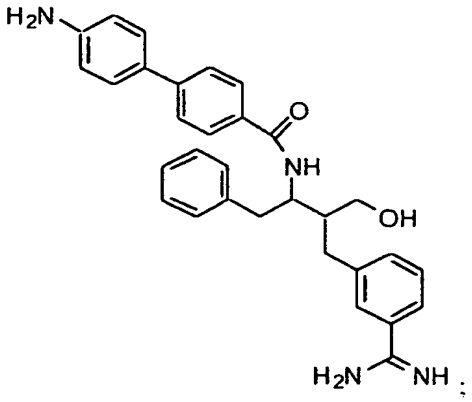


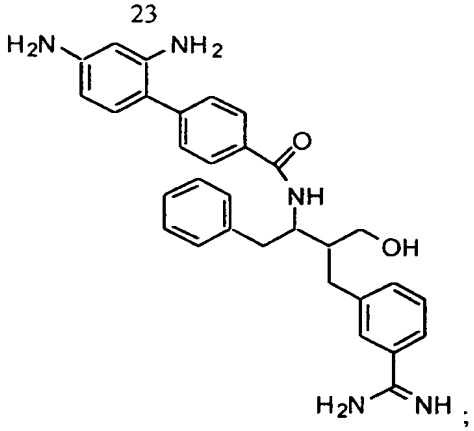


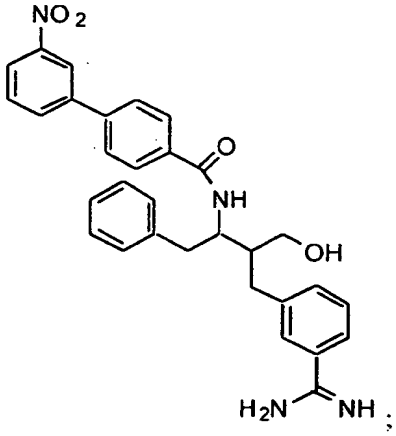


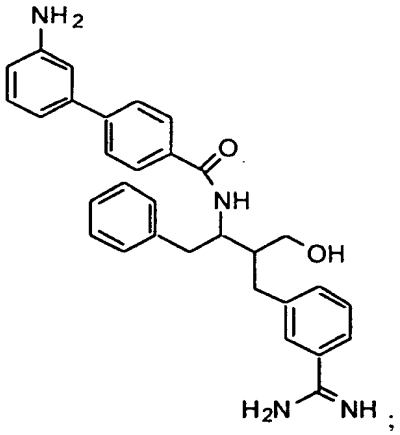


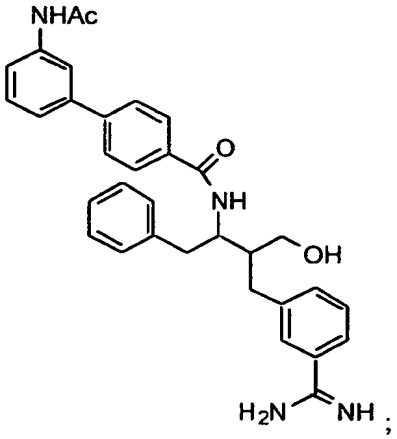
5

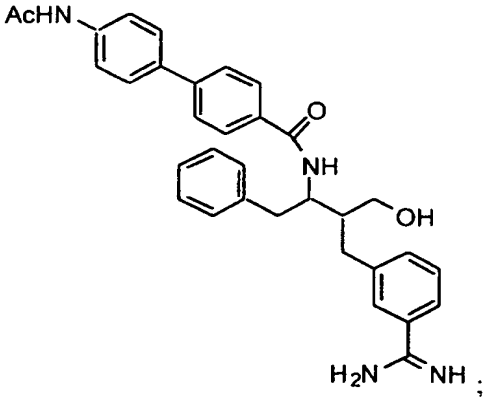




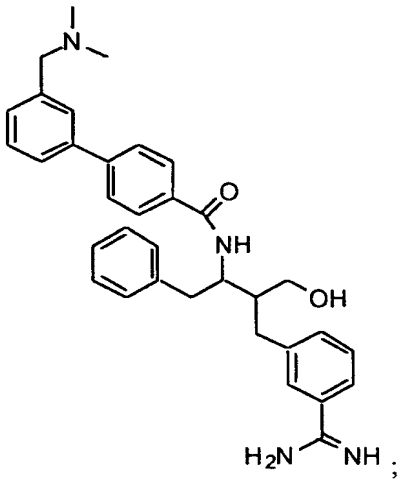




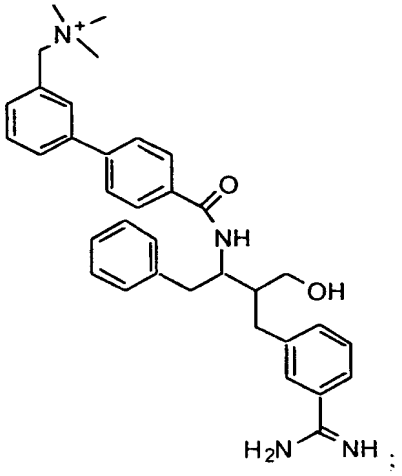




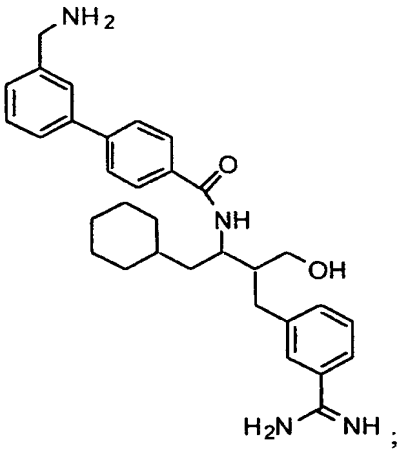
5


N
O
NH
OH
H2N
NH

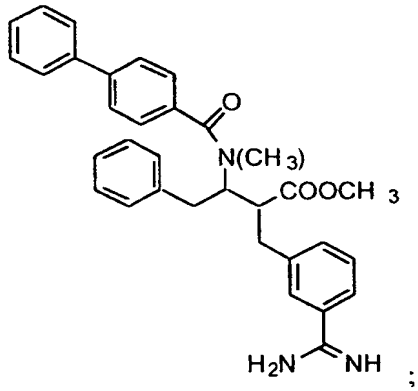
;


N+
O
NH
OH
H2N
NH

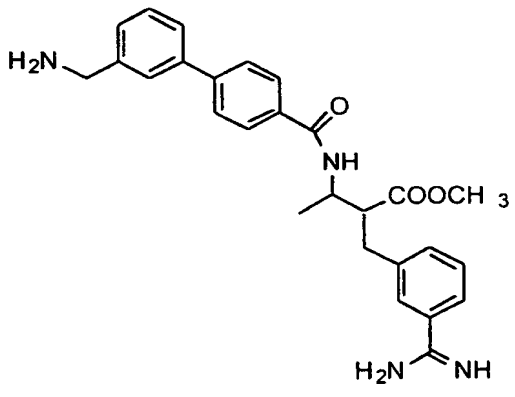
;


NH2
O
NH
OH
H2N
NH

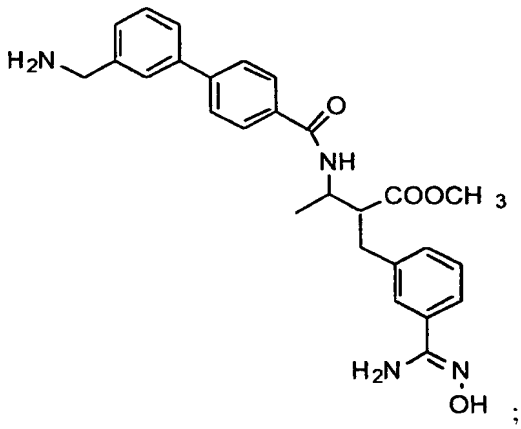
;


O
N(CH3)
COOCH3
H2N
NH

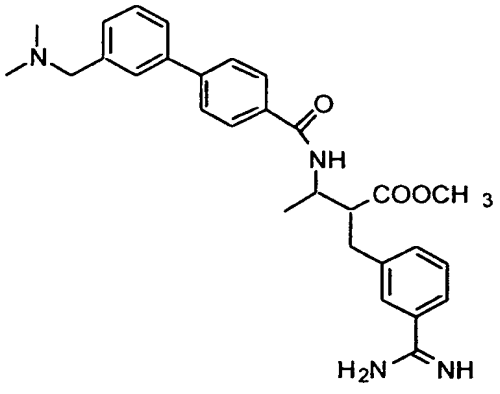
;


H2N
O
NH
COOCH3
H2N
NH

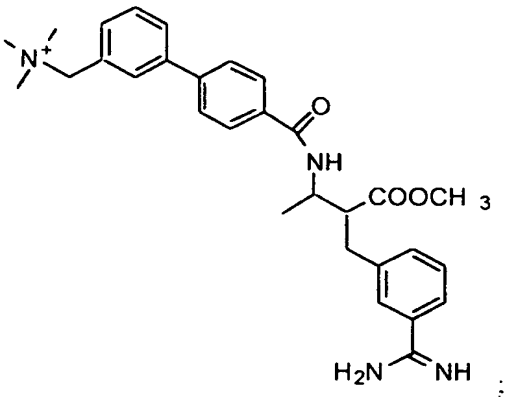
:


H2N
O
NH
COOCH3
H2N
N
OH

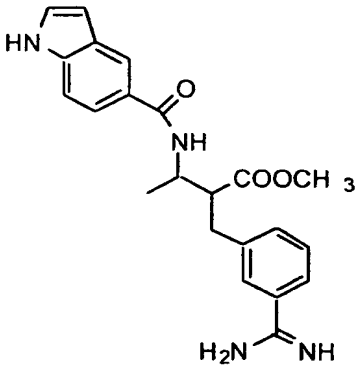
;



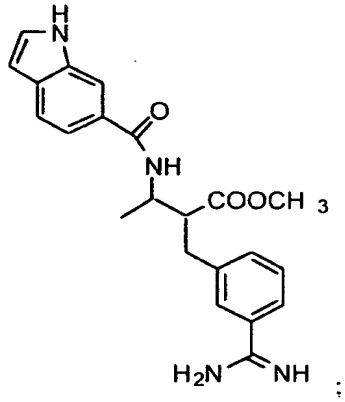
;



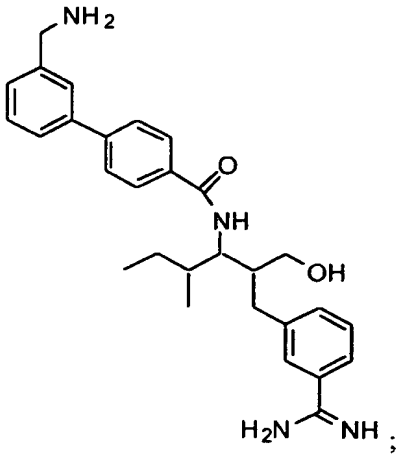
;



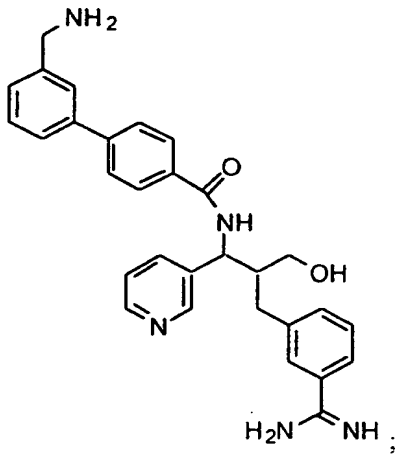
;



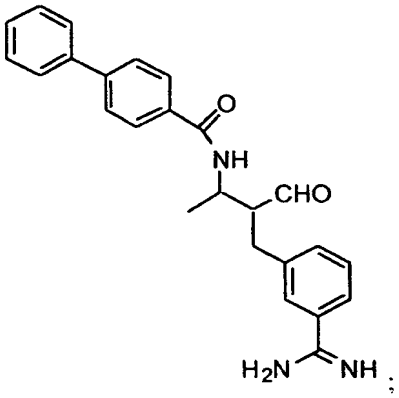
;

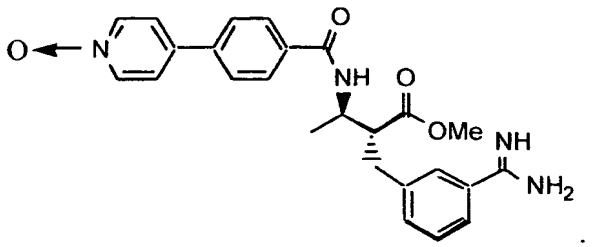


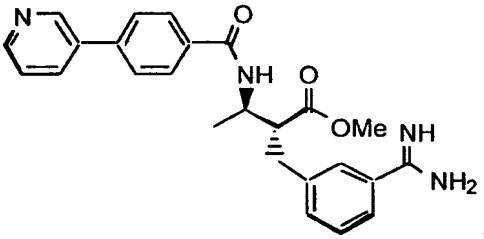
;

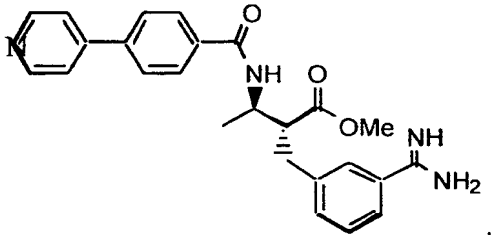


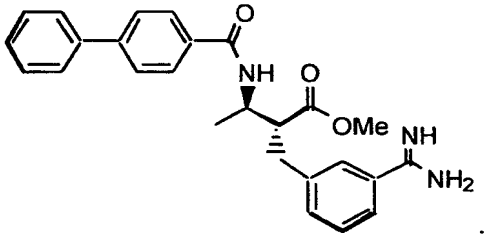
;

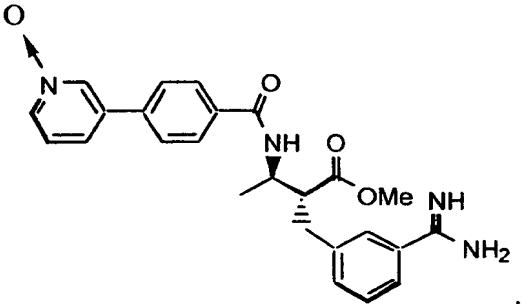

;

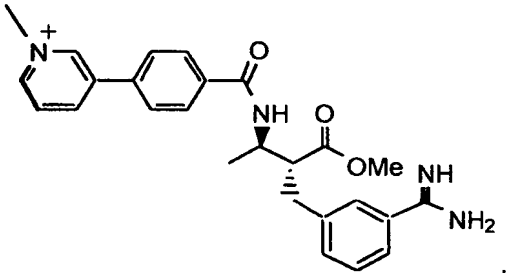

;

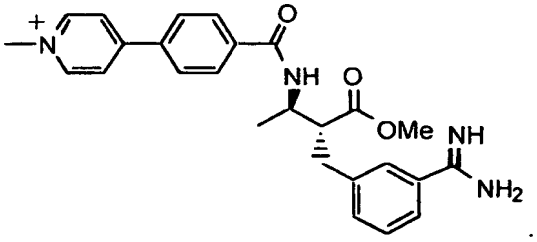

;

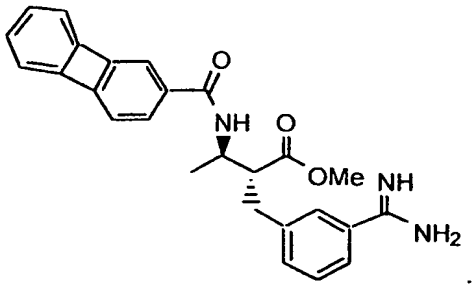

;

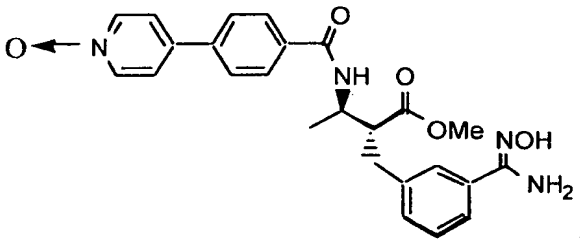

;

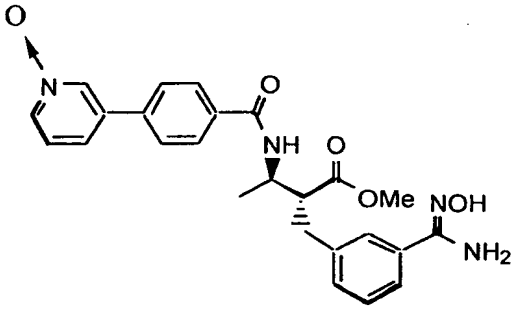

;

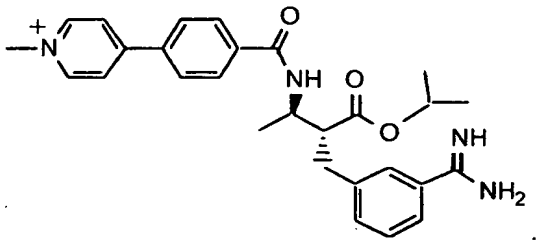

;

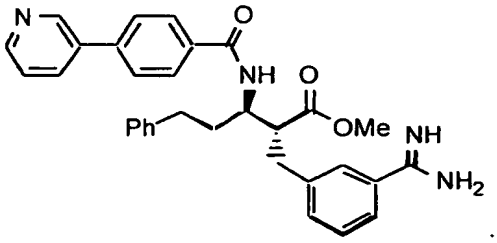

;

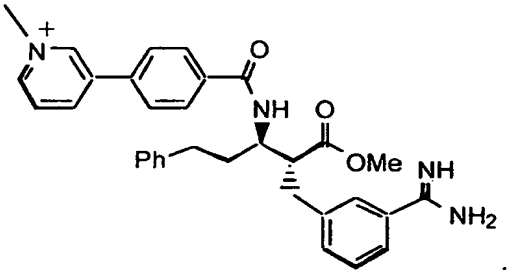

;

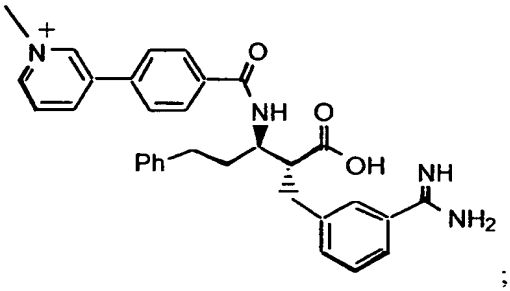

;

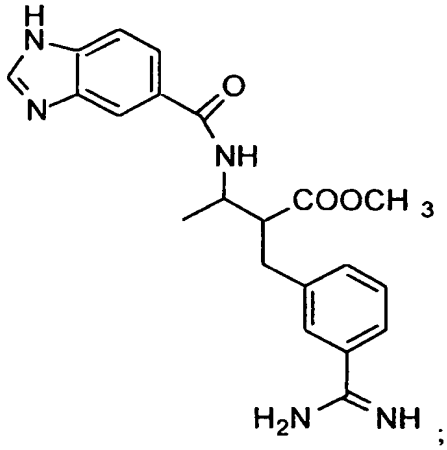

;

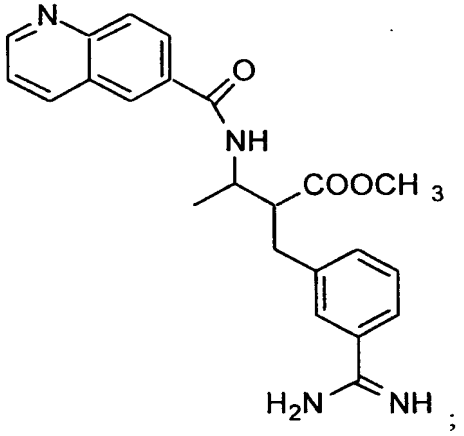

;


;

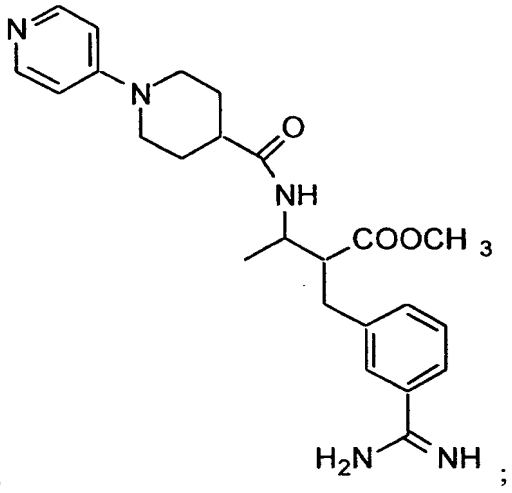

;


;

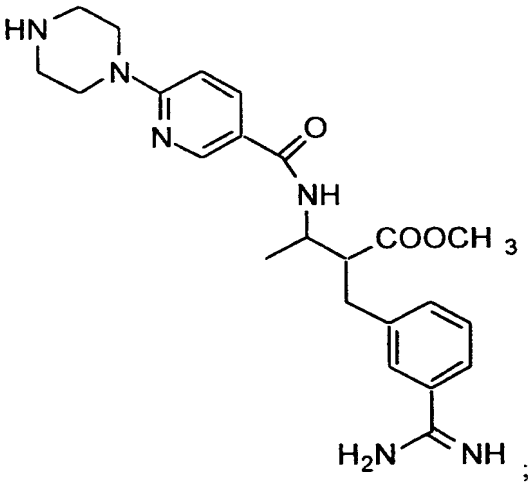

;



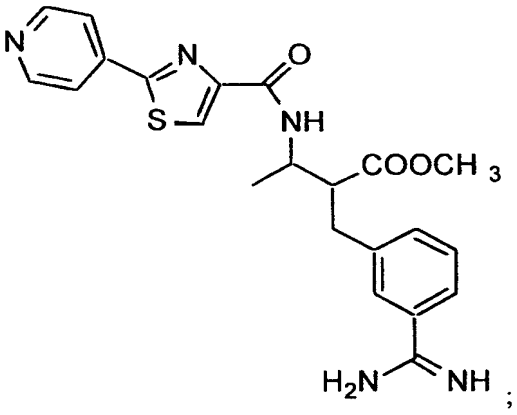
;



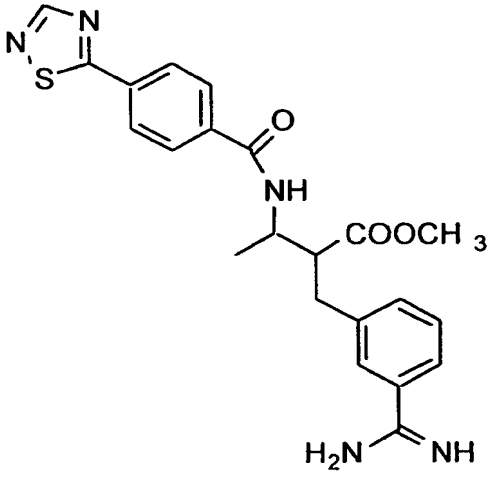
;



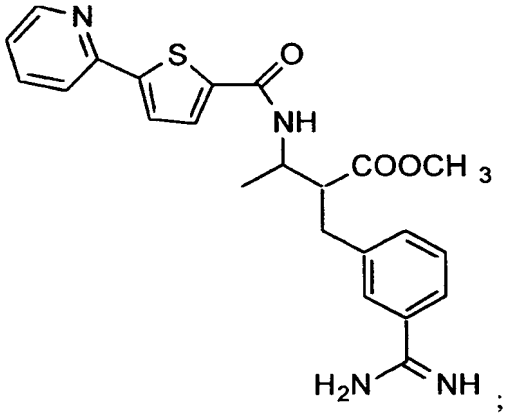
;



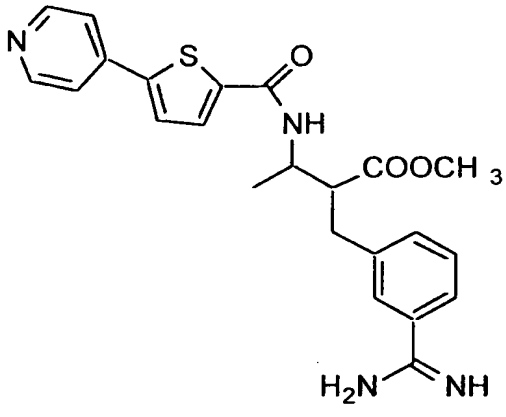
;

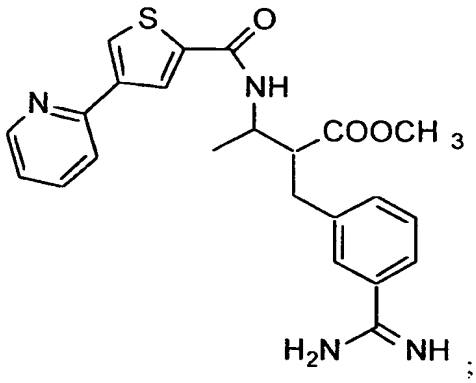


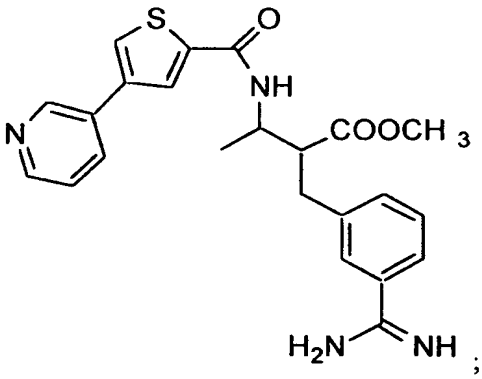
;

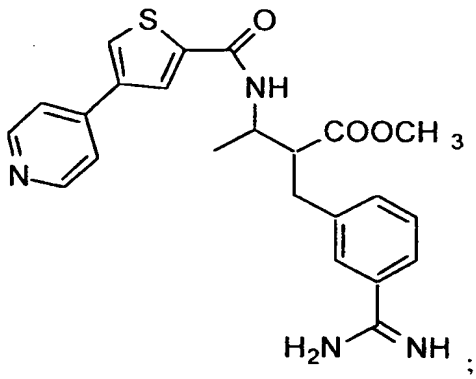


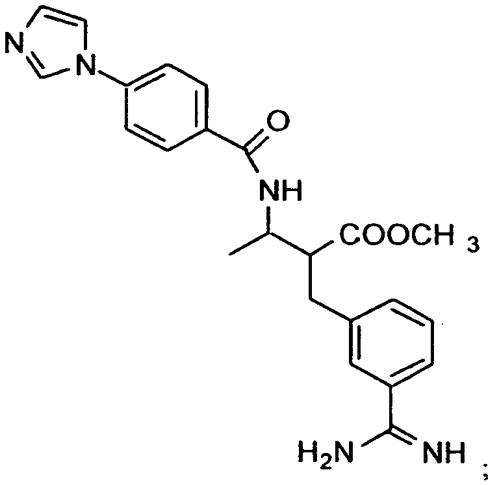
;

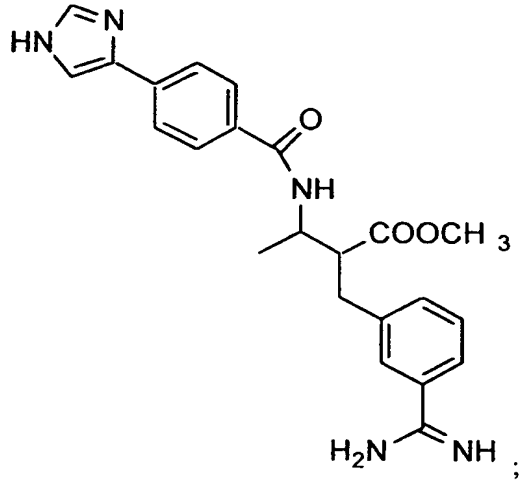




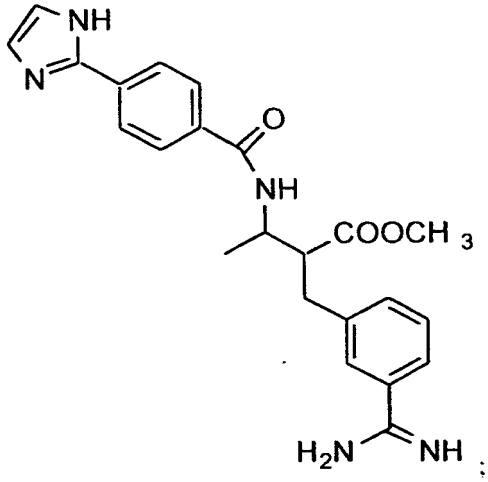


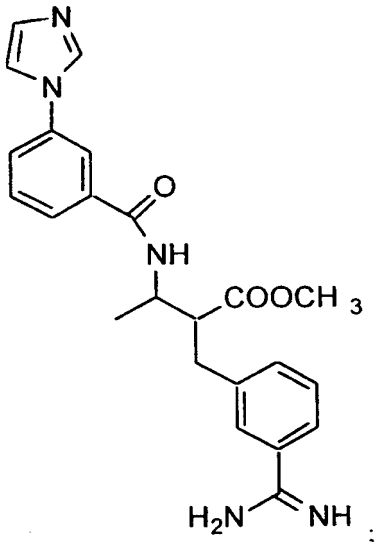


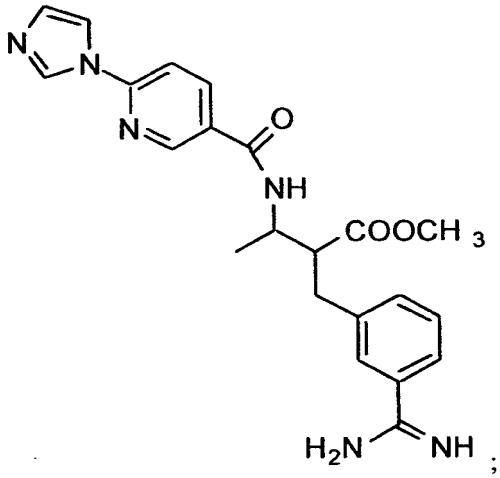


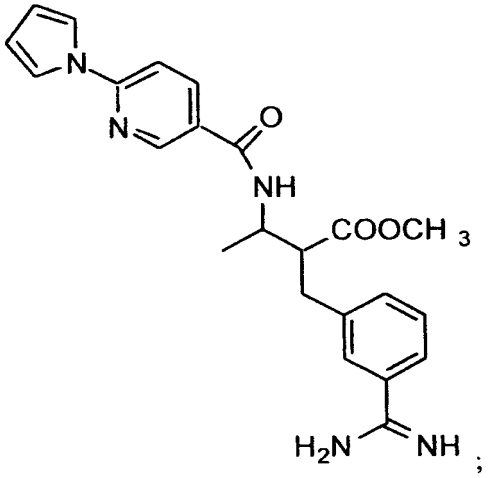


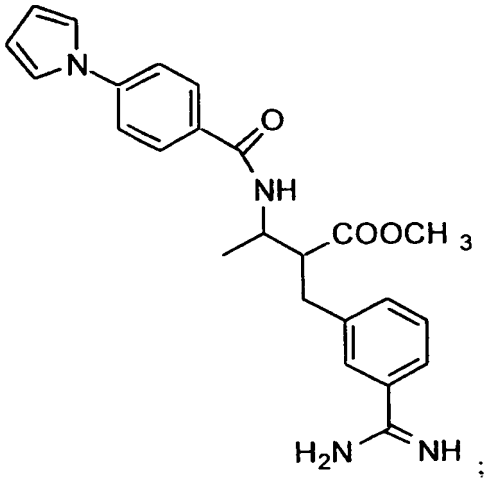
5

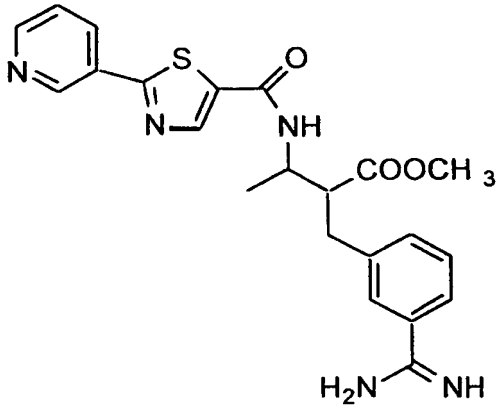


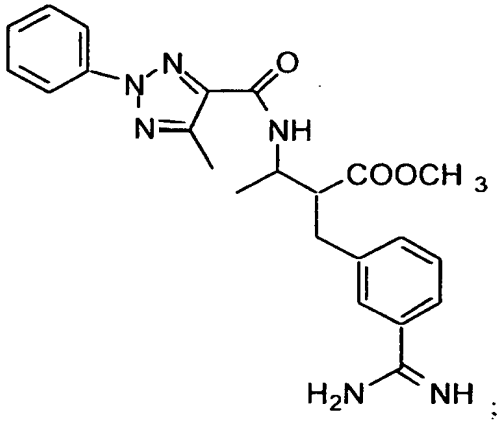


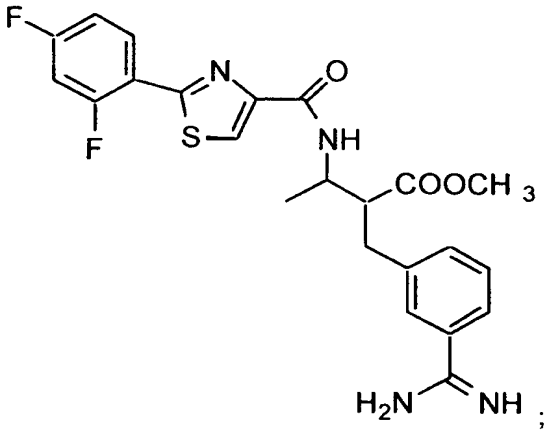


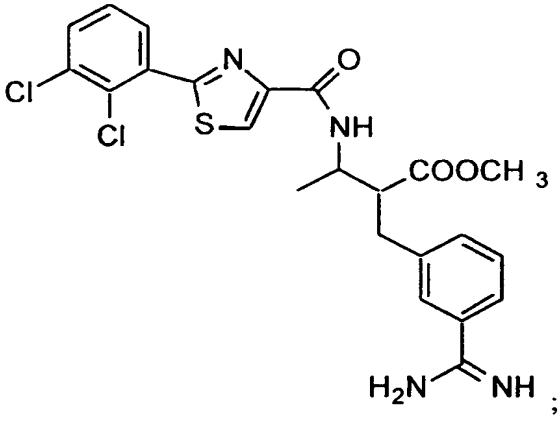


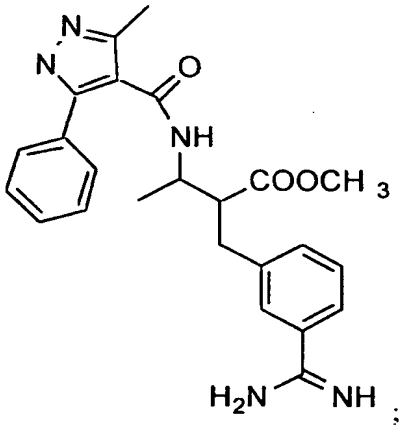




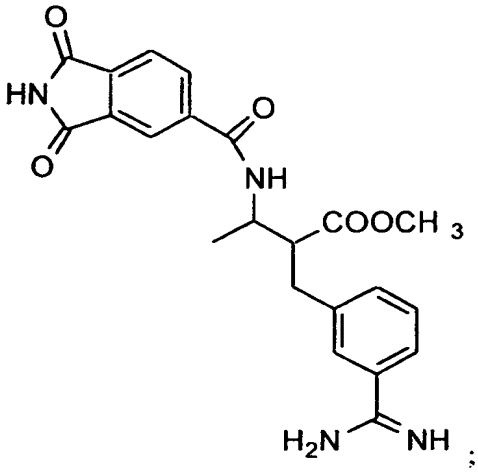


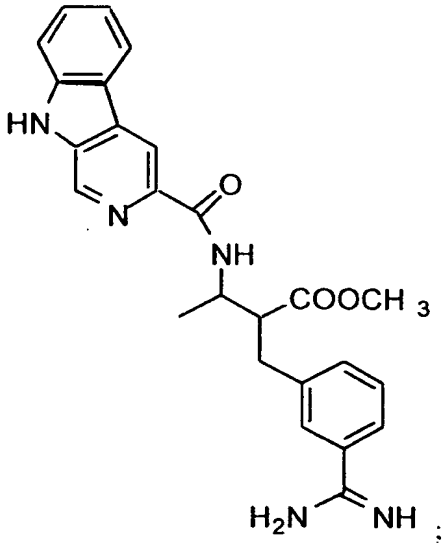


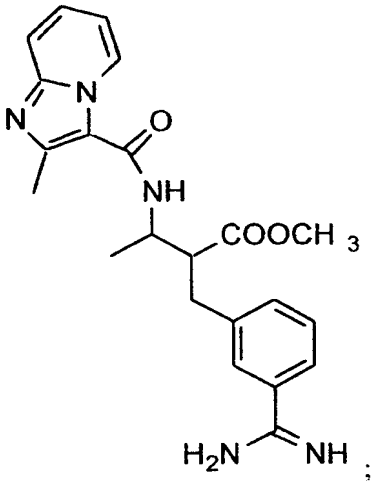


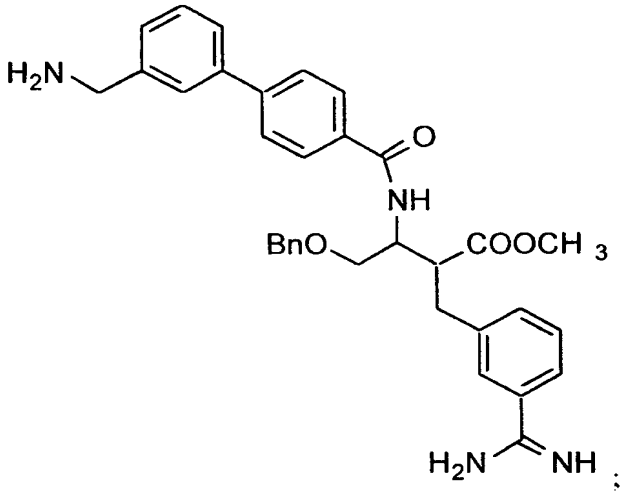


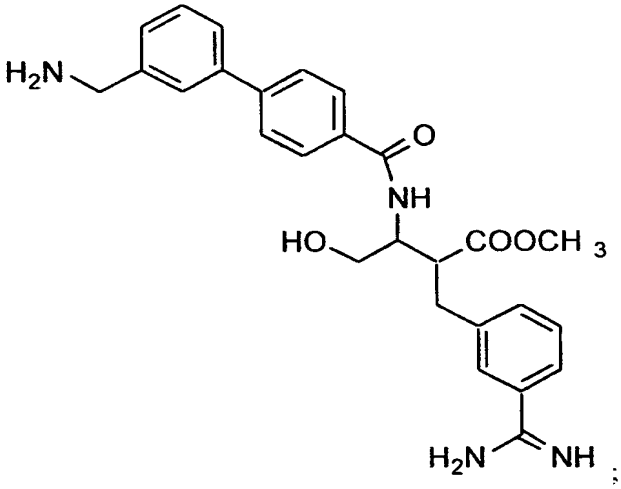
5

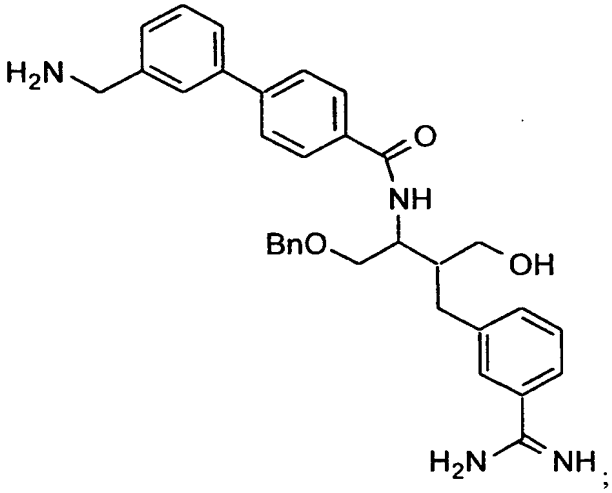


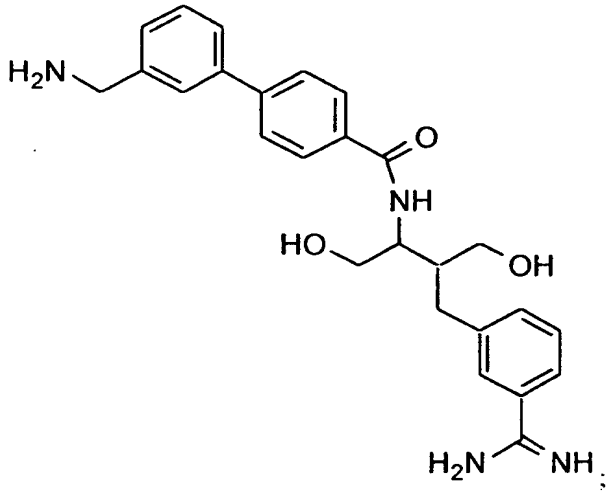


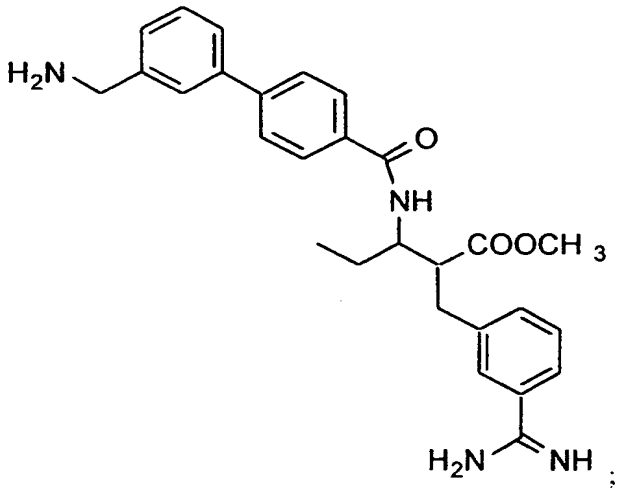


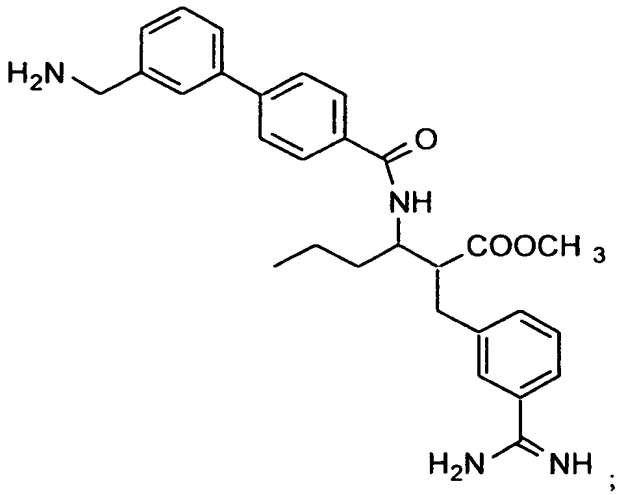


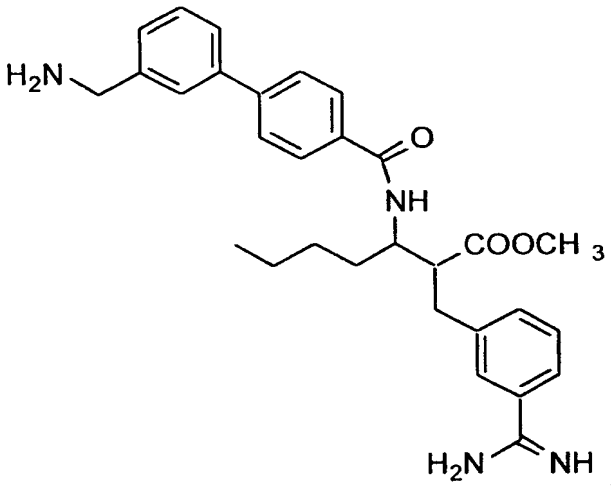


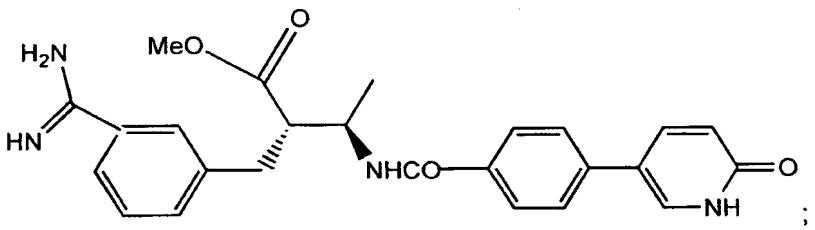


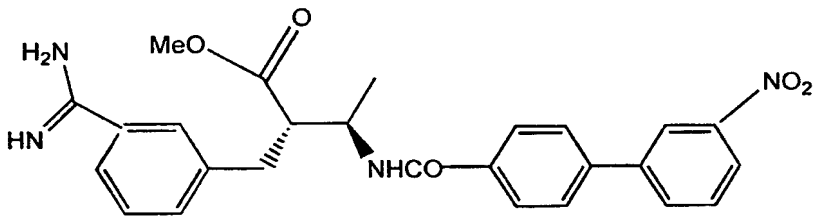


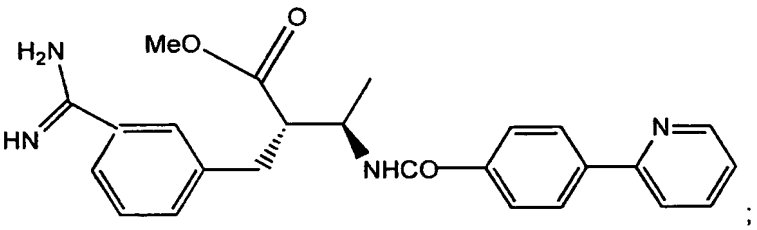


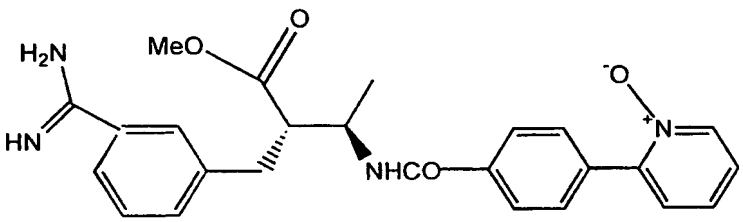


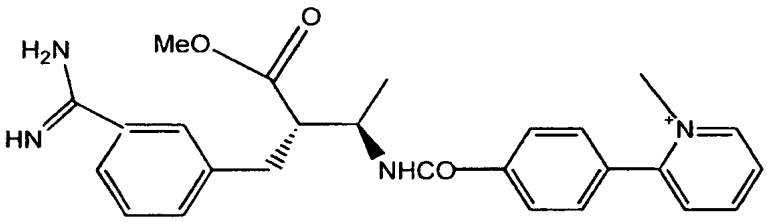




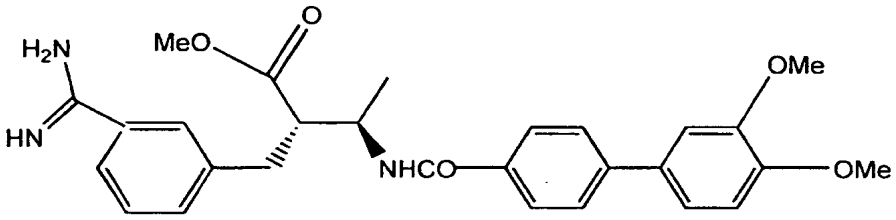




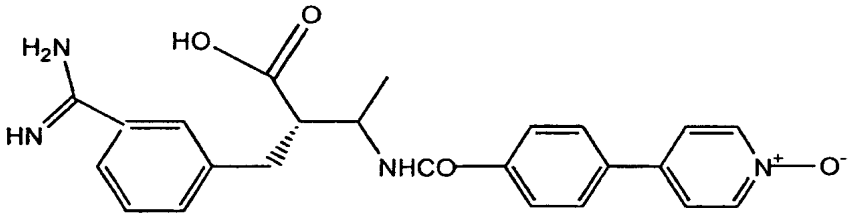



H2N
MeO
O
HN
NHCO
N+

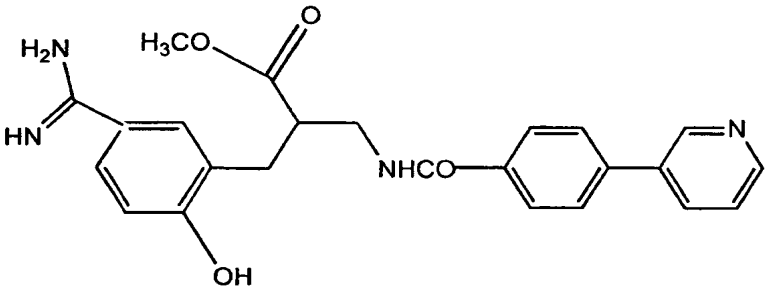
;


H2N
MeO
O
HN
NHCO
OMe
OMe

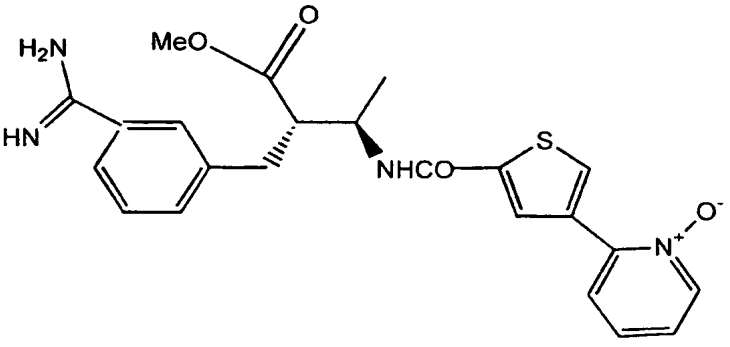
;


H2N
HO
O
HN
NHCO
N+
O-

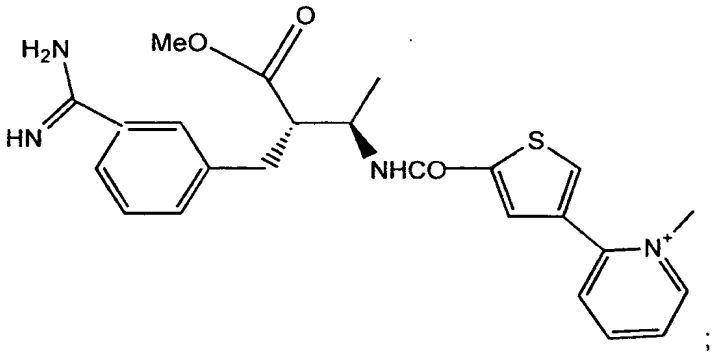
;


H2N
H3CO
O
HN
NHCO
N
OH

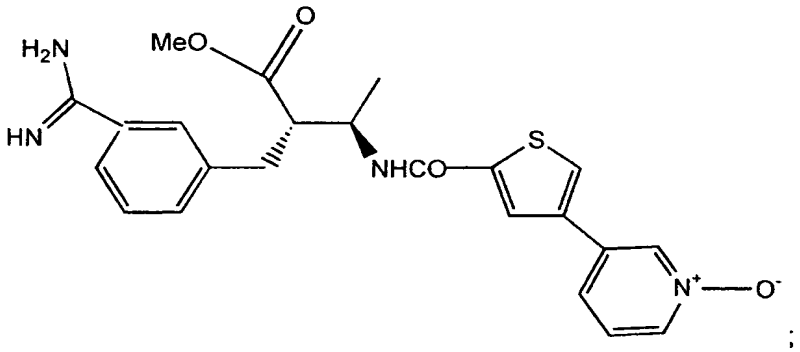
;


H2N
MeO
O
HN
NHCO
S
N+
O-

;

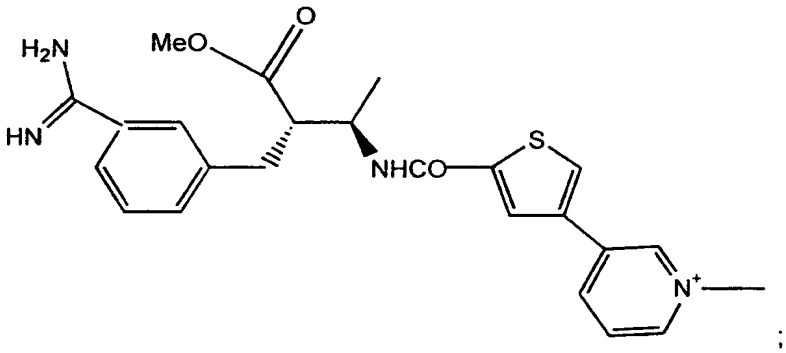


;

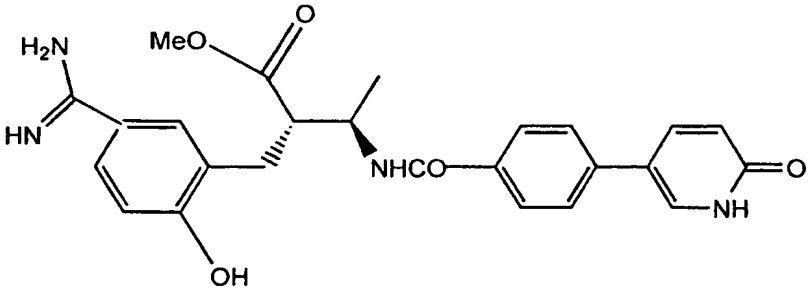


;

5



;



;

(Z)-N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)allyl]-4-pyridin-3-ylbenzamide;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-pyridin-3-yl)-benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(1-oxy-pyridin-4-yl)-benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(6-oxo-1,6-dihydropyridin-3-yl-benzamide trifluroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(pyridazin-4-yl)benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-7-chlorobenzothiophene-2-carboxamide trifluroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide trifluoroacetate;

(E)-Biphenyl-4-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-pyridin-3-yl-benzamide ditrifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-pyridin-4-yl-benzamide ditrifluoroacetate;

(E)-Biphenyl-3,4'-dicarboxylic acid 3-amide 4'-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide} trifluoroacetate;

(E)-4-tert-Butyl-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-benzamide trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(3H-imidazol-4-yl)-benzamide ditrifluoroacetate;

(E)-Biphenyl-4,4'-dicarboxylic acid 4'-amide 4-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide} trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(1H-imidazol-2-yl)-benzamide ditrifluoroacetate;

(E)-3-Oxo-2,3-dihydro-thieno[3,2-c]pyridazine-6-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide trifluoroacetate;

(E)-5-Pyridin-2-yl-thiophene-2-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide ditrifluoroacetate;

Biphenyl-4-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-propyl]-amide trifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate;

Biphenyl-3,4'-dicarboxylic acid 3-amide 4'-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)-propyl]-amide} trifluoroacetate;

4-tert-Butyl-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-propyl]-benzamide trifluoroacetate;

[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(3H-imidazol-4-yl)-benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(1H-imidazol-2-yl)-benzamide ditrifluoroacetate;

5-Pyridin-2-yl-thiophene-2-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide ditrifluoroacetate; and

N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-piperidin-4-yl-benzamide ditrifluoroacetate.

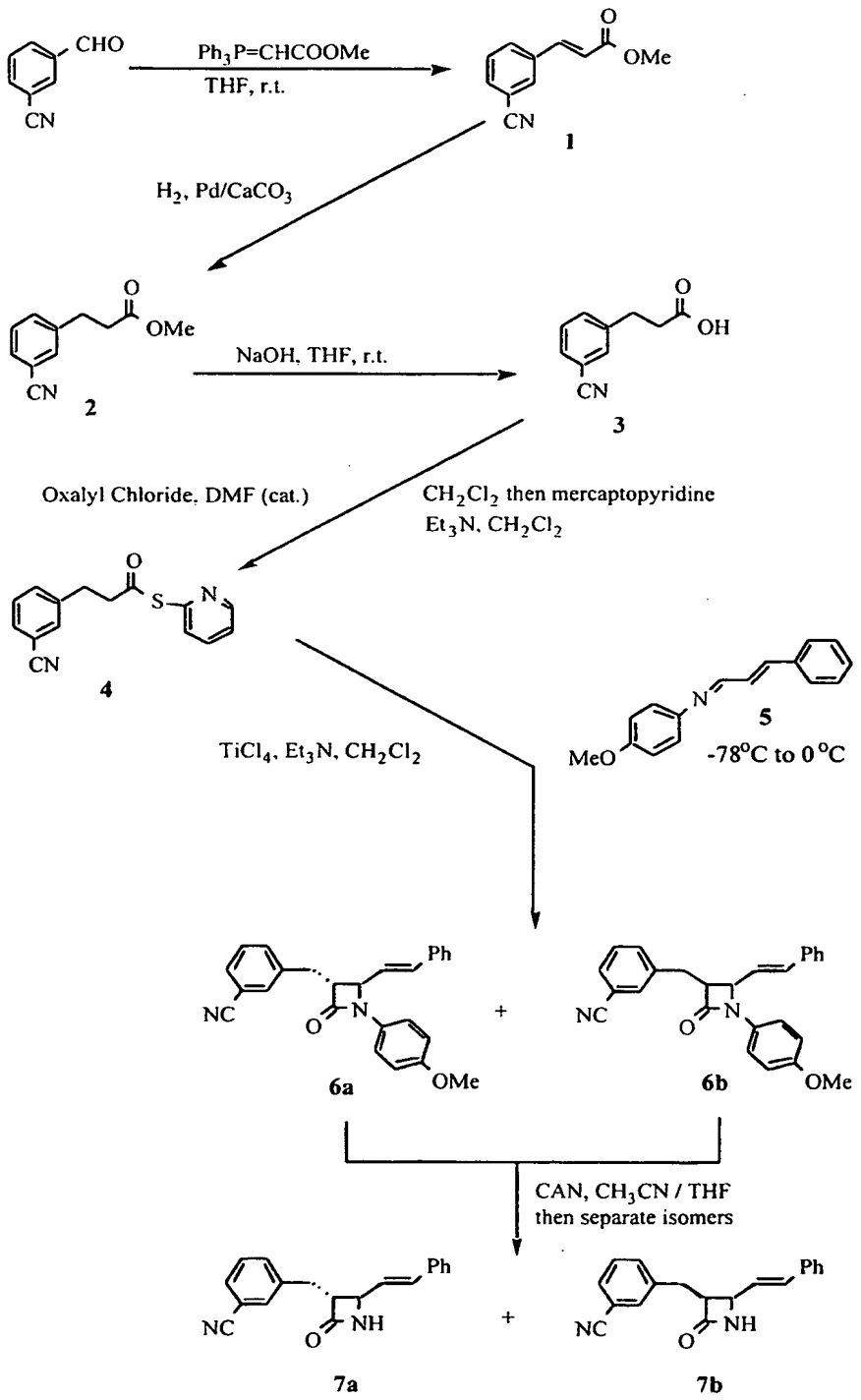
More preferred species according to the invention are compounds 188, 209-211, 217, 221, 235, 280-281, 284-285, 301, 304-305, 310, 314, 325, 344 and 346.

It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein.

Compounds of Formula I may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to this invention herein.

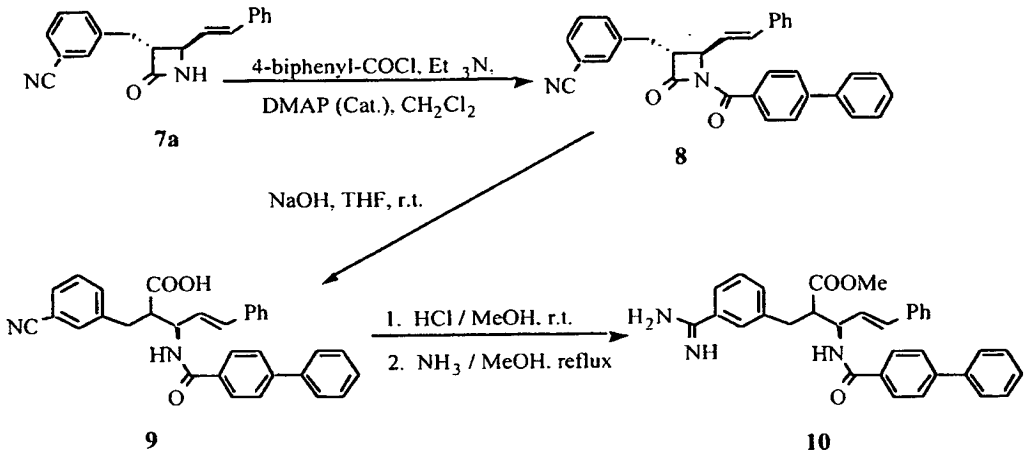
Scheme A exemplifies a general method for preparing intermediates for use in preparing compounds of formula I according to the invention.

SCHEME A



Scheme B exemplifies a general method for converting the intermediates prepared according to Scheme A to compounds of formula I according to the invention.

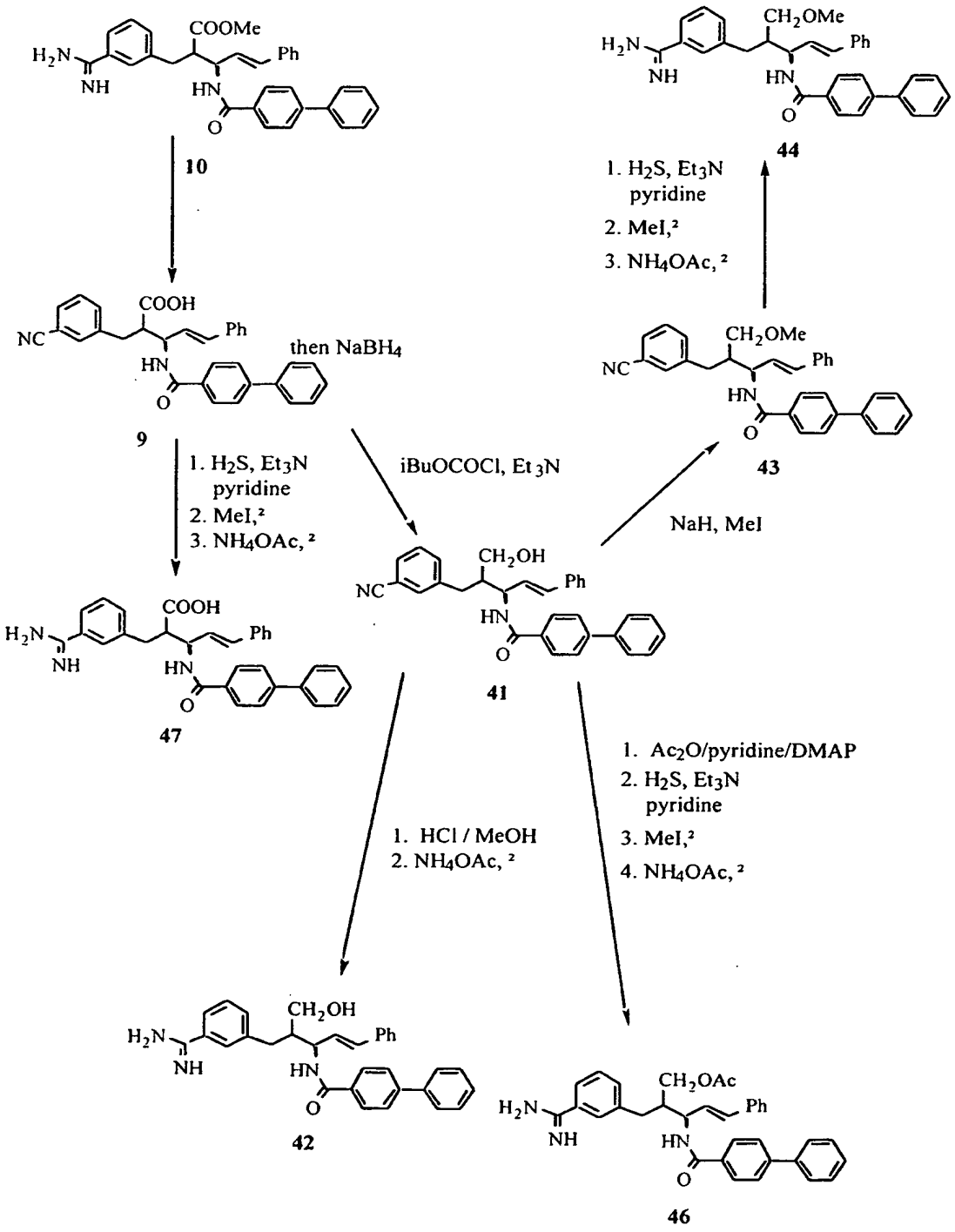
SCHEME B



Scheme C exemplifies a general method for effecting interconversions between compounds of formula I according to the invention.

41

SCHEME C

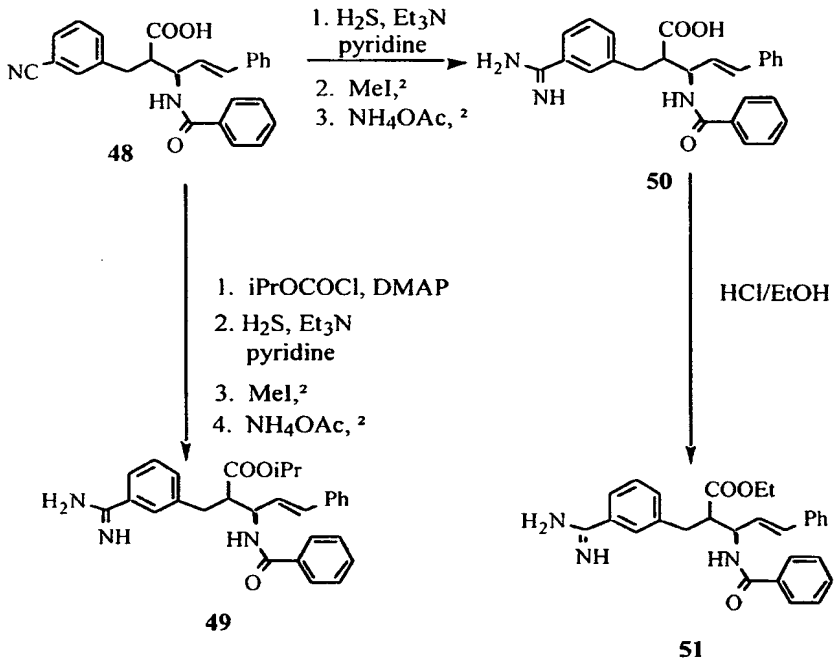


In addition, the compounds of formula 1 wherein R_3 is hydroxymethyl may be converted to the corresponding thiolmethyl compounds by treating the alcohol with an alkyl or aryl sulfonyl halide and

displacing the alkyl or aryl sulfonate with NaSH. the thiolmethyl compounds may then be alkylated or acylated to give other compounds within the scope of the invention.

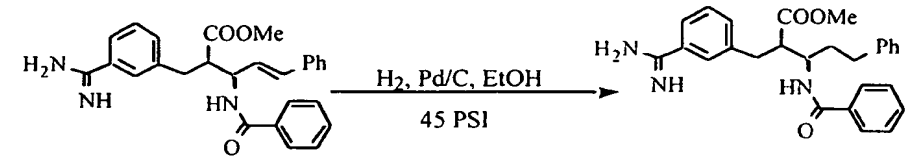
Scheme D exemplifies a general method for converting a nitrile intermediate to a compound of formula I and additional general methods for effecting interconversions between compounds of formula I according to the invention.

SCHEME D

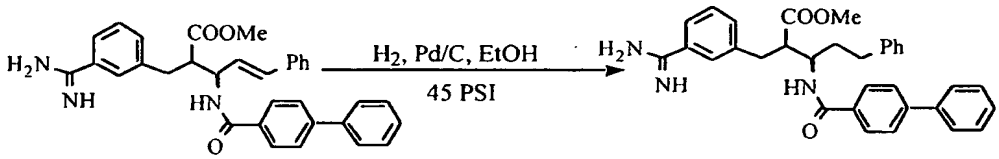


Scheme E exemplifies an additional general method for effecting interconversions between compounds of formula I according to the invention.

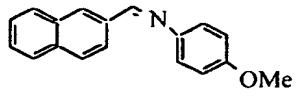
SCHEME E



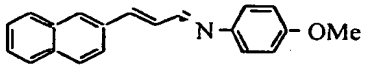
11 52



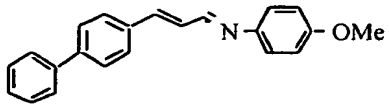
10 53



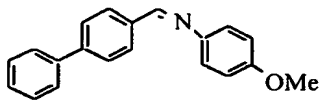
33



34



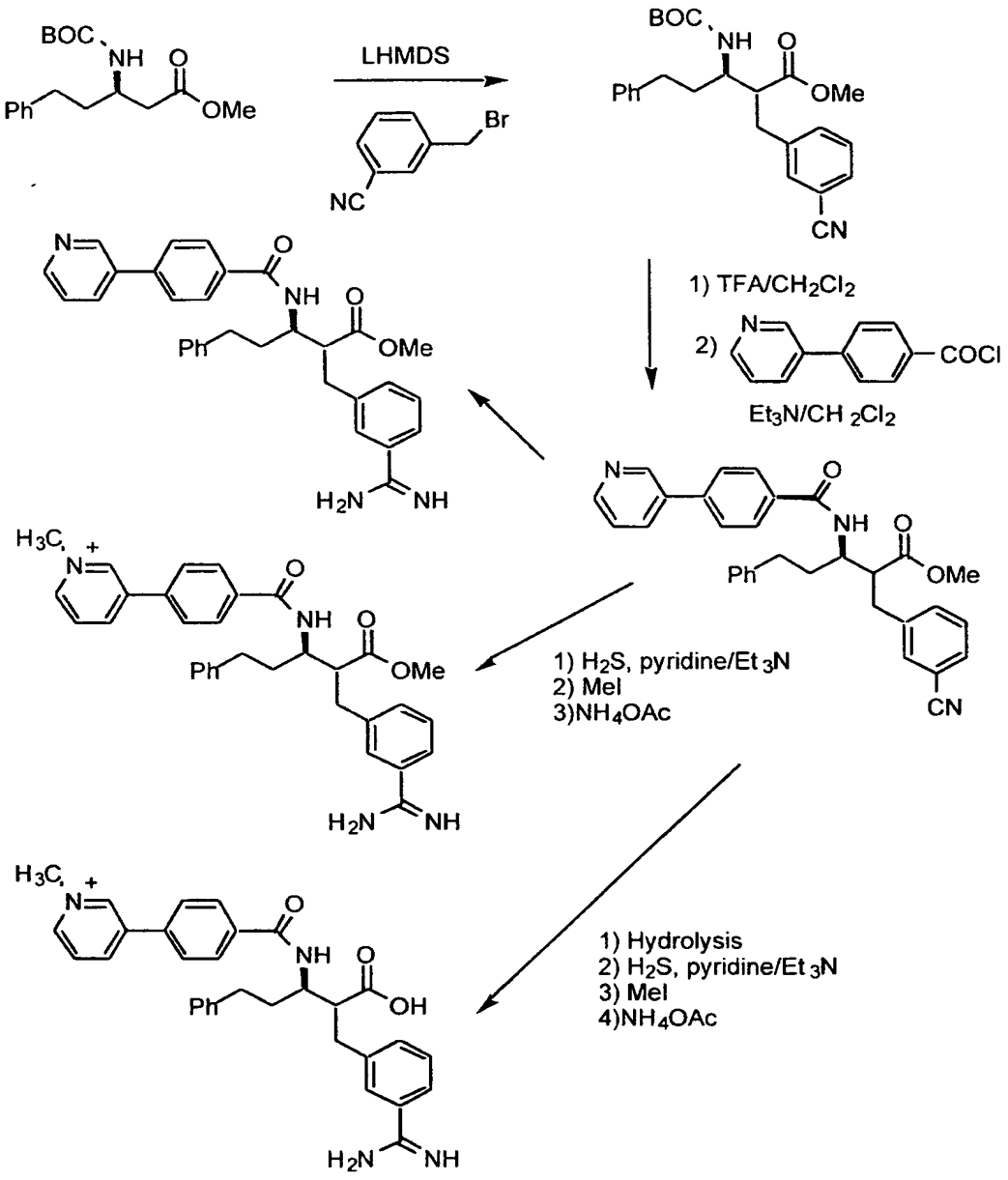
35



36

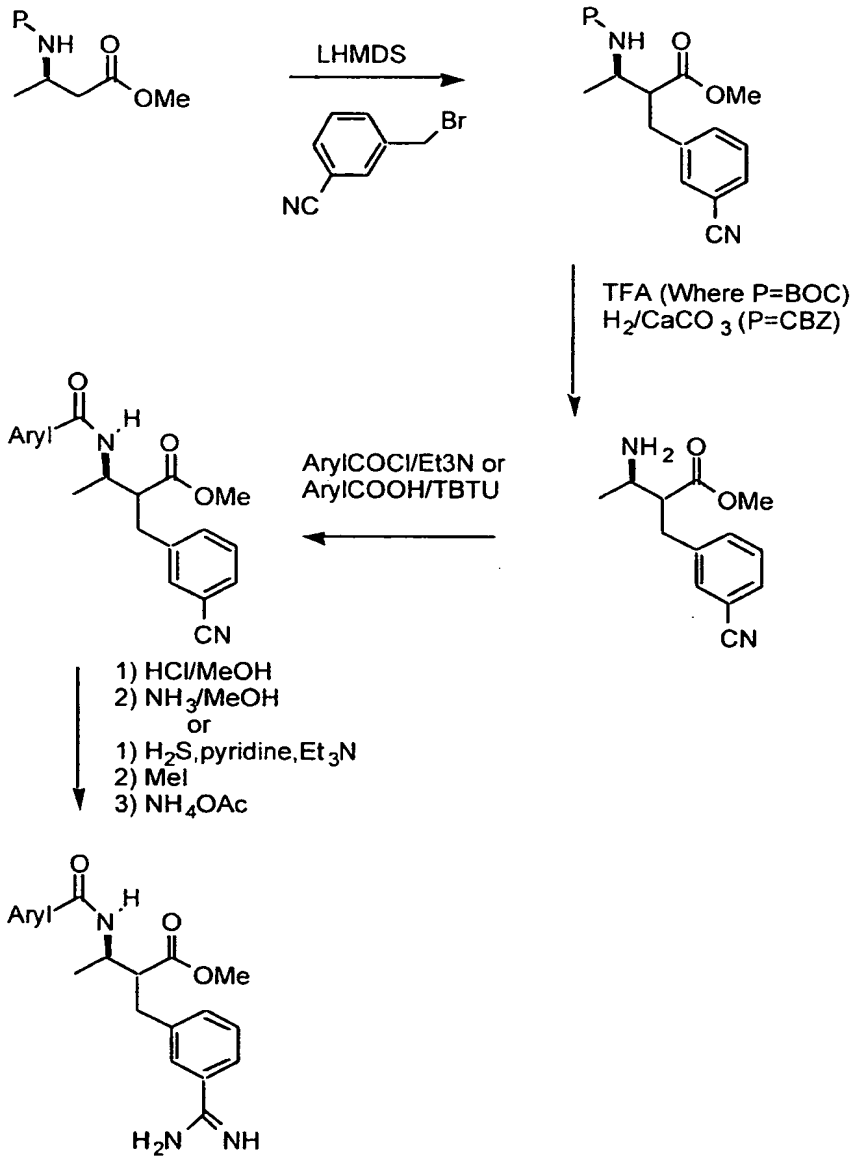
Scheme F exemplifies a general method for preparing compounds according to the present invention wherein R_4 of formula I is optionally substituted phenethyl.

Scheme F



Scheme G exemplifies a general method for preparing compounds according to the present invention wherein R_4 of formula I is methyl.

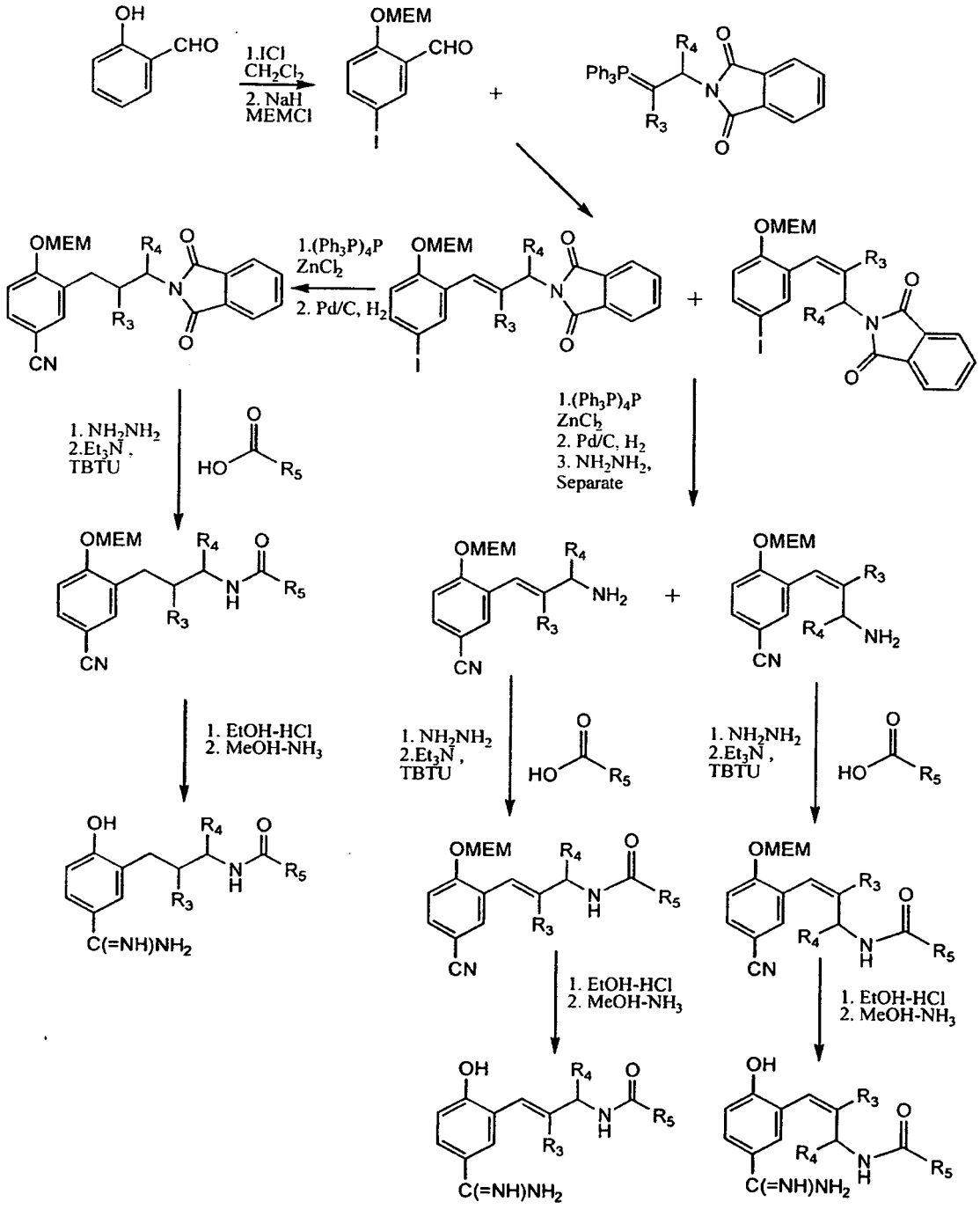
Scheme G



Scheme H exemplifies a general method for preparing compounds according to the present invention.

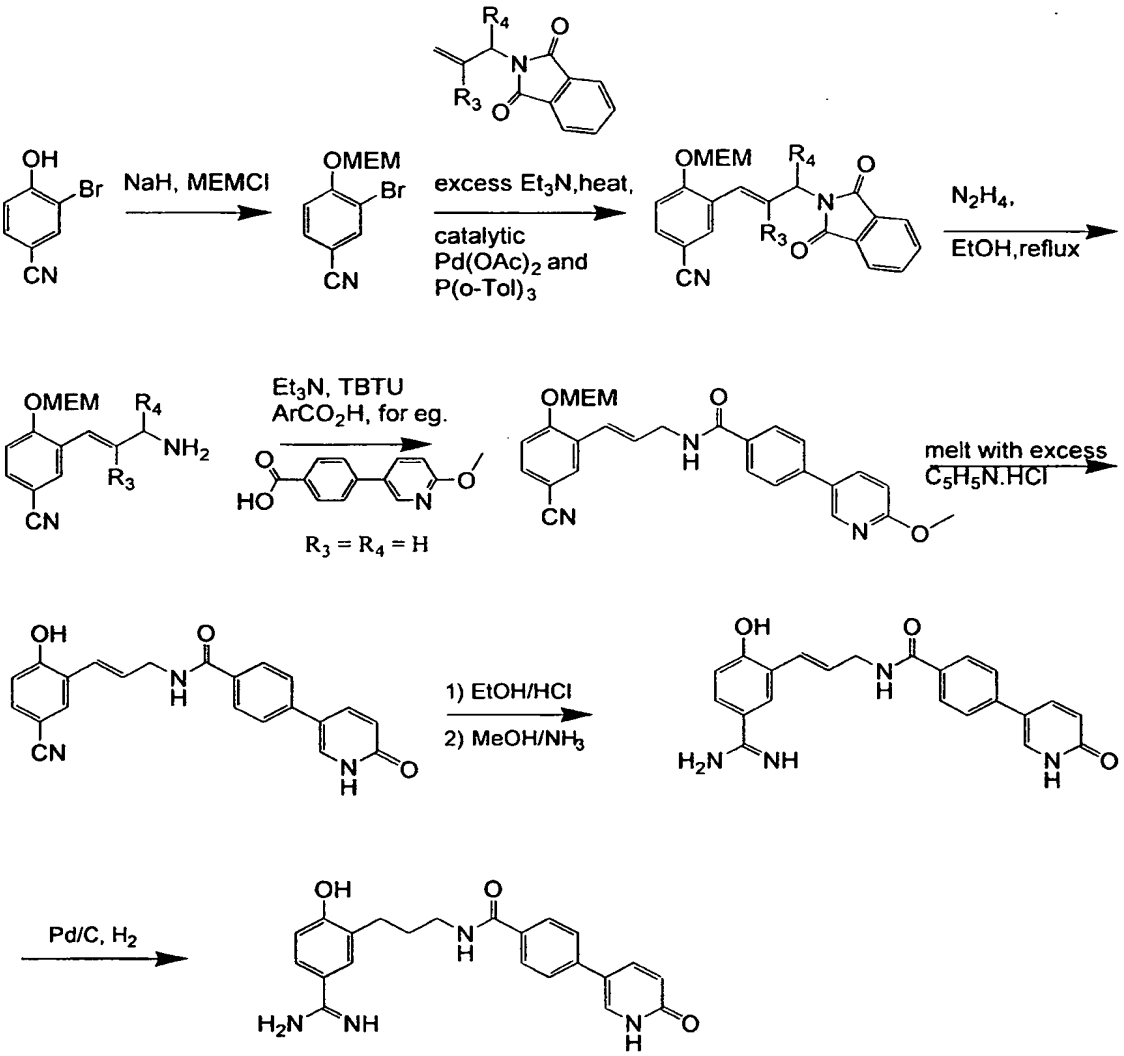
Scheme H exemplifies a general method for preparing compounds according to the present invention.

Scheme H



Scheme I exemplifies a general method for preparing compounds according to the present invention.

Scheme I



It will be apparent to those skilled in the art that certain compounds of formula I can exhibit isomerism, for example geometrical isomerism, e.g., E or Z isomerism, and optical isomerism, e.g., R or S configurations. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl moieties. Individual geometrical isomers and stereoisomers within formula I, and their mixtures, are within the scope of the invention.

Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylene-bis-B-hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

According to a further feature of the invention, acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form

inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

Pharmaceutically acceptable salts also include quaternary lower alkyl ammonium salts. The quaternary salts are prepared by the exhaustive alkylation of basic nitrogen atoms in compounds, including nonaromatic and aromatic basic nitrogen atoms, according to the invention, i.e., alkylating the non-bonded pair of electrons of the nitrogen moieties with an alkylating agent such as methylhalide, particularly methyl iodide, or dimethyl sulfate. Quaternarization results in the nitrogen moiety becoming positively charged and having a negative counter ion associated therewith.

As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds of this

invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein there is not an acid labile group.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

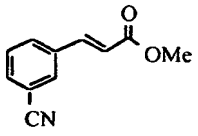
The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents, or by methods according to this invention.

The present invention is further exemplified but not limited by the following illustrative examples which illustrate the preparation of the compounds according to the invention.

In the nuclear magnetic resonance spectra (NMR) the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significance: s=singlet; d=doublet; t=triplet; m=multiplet; dd=doublet of doublets; ddd=doublet of doublets of doublets; dt=doublet of triplets, b=broad.

EXAMPLE 1

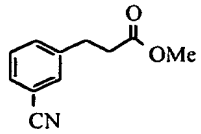
Compound 1



To a stirred solution of 3-cyanobenzaldehyde (20 g; 153 mmol) in 100 mL of dry THF under N_2 at room temperature is added methyl (triphenylphosphoranylidene)acetate (61.2 g; 183 mmol). The mixture is allowed to stir overnight at room temperature and then concentrated *in vacuo*. The crude residue is chromatographed (40% EtAc:Hexane) to give 27.3 g (96%) of the acrylate 1. ^1H NMR ($CDCl_3$, δ): 7.43 - 7.8 (m, 5H), 6.47 (d, J = 12 Hz, 1H), 3.8 (s, 3H).

EXAMPLE 2

Compound 2

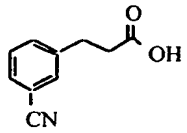


To a stirred solution of compound 1 (27.33 g) in 150 mL of EtOH is added 2 g of 10% $Pd/CaCO_3$. The resulting mixture is hydrogenated under 45 PSI H_2 on a Parr shaker for 8 hours at room temperature. The mixture is then filtered through a plug of celite and the filtrate concentrated *in vacuo* to give 26.93 g (98 %) of 2 as a clear oil.

^1H NMR ($CDCl_3$, d): 7.33 - 7.72 (m, 4H), 3.66 (s, 3H), 2.97 (t, J = 7.8 Hz, 2H), 2.62 (t, J = 7.8 Hz, 2H).

EXAMPLE 3

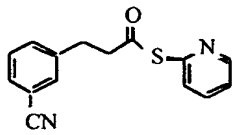
Compound 3



To a stirred solution of compound 2 (16.8 g; 89 mmol) in 200 mL of THF:MeOH (2:1) at room temperature is added 9 mL of 10 N NaOH solution dropwise. After 2h. most of the solvent is removed in vacuo and 30 mL of 5N HCl is added. The resulting mixture is extracted several times with EtOAc. The combined extracts are dried ($MgSO_4$), filtered and concentrated to give 9.8 g (63%) of pure acid 3 as a white solid. ^1H NMR ($CDCl_3$, δ): 7.35 - 7.55 (m, 4H), 2.98 (t, J = 7.9 Hz, 2H), 2.7 (t, J = 7.9 Hz, 2H).

EXAMPLE 4

Compound 4

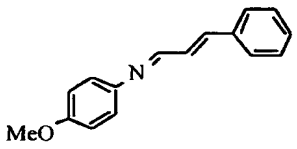


To a stirred solution of the carboxylic acid 3 (8.2 g; 47 mmol) an DMF (0.5 mL) in dry CH_2Cl_2 under N_2 at room temperature is added oxalyl chloride (6.1 mL; 70 mmol) dropwise. After 1 hour, gas evolution ceased and the solvent and excess oxalyl chloride is removed *in vacuo*. The residue is redissolved in 100 mL of dry CH_2Cl_2 and cooled to 0°C. Mercaptopyridine (5.6 g; 50 mmol) is added followed by triethylamine (7.9 mL; 56 mmol). The mixture is allowed to warm to r.t. and stirred for 1 hour. The mixture is diluted with CH_2Cl_2 and washed with 1 N NaOH. The organic layer is dried ($MgSO_4$), filtered and concentrated. The residue is chromatographed (eluent = 50% EtOAc:Hexane) to

give 5.12 g (84%) of the thioester 4 as a yellow oil. ^{1}H NMR ($CDCl_3$, δ): 8.63 (d, J = 9 Hz, 1H), 7.7 - 7.8 (m, 1H), 7.27 - 7.62 (m, 6H), 3.05 (s, 4H).

EXAMPLE 5

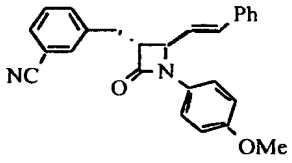
Compound 5



Magnesium sulfate (19.55 g; 162 mmol) is added to a stirred solution of cinnamaldehyde (10.2 mL; 81 mmol) and *p*-anisidine (10 g; 81 mmol) in 200 mL of CH_2Cl_2 under N_2 at 0°C. After 4 hours, the mixture is filtered and the filtrate concentrated to give 18.87 g (98 %) of the imine compound 5 as a gold: brown solid. ^{1}H NMR ($CDCl_3$, δ): 8.28 (m, 1H), 7.52 (m, 2H), 7.38 (m, 3H), 7.2 (m, 2H), 7.12 (m, 2H), 6.93 (m, 2H), 3.82 (s, 3H).

EXAMPLE 6

Compound 6

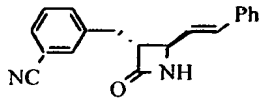


To a stirred solution of the thioester 5 (7 g; 26 mmol) in dry CH_2Cl_2 (120 mL) under N_2 at -78°C is added $TiCl_4$ solution (26.1 mL of 1 M solution in CH_2Cl_2). After 15 minutes, triethylamine (3.6 mL; 26 mmol) is added dropwise. The resulting mixture is allowed to stir for 1/2h at -78°C and then a solution of imine 1 (4.42 g ; 19 mmol in 20 mL CH_2Cl_2) is added dropwise. The mixture is then warmed to 0°C. After 1.5 hours at this temperature, the mixture is quenched with saturated $NaHCO_3$ solution and partitioned with water. The organic layer is washed with 1 N NaOH, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product is chromatographed (eluent = 40% EtOAc:hexane) to give 2.42 g (32 %) of a 5:1 mixture of trans- /cis- b -lactam 6a and 6b as a gum.

Major trans-Isomer 6a: ^{1}H NMR ($CDCl_3$, δ): 7.2 - 7.6 (m, 11H), 6.8 (d, J = 11 Hz, 2H), 6.65 (d, J = 15.8 Hz, 1H), 6.2 (dd, J = 15.8, 7.9 Hz, 1H), 4.32 (m, 1H), 3.72 (s, 3H), 3.42 (m, 3H).

EXAMPLE 7

Compound 7



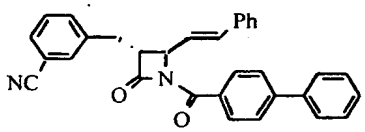
To a stirred solution of 6a, 6b (1.5 g; 3.8 mmol) in 60 mL of THF/CH_3CN (1/3) at -20°C is added a solution of ceric ammonium nitrate (CAN, 3.13g; 5.7 mmol in 10 mL water). After 15 minutes, another 1.5 g of CAN in 5 mL of water is added. After a further 30 minutes, the mixture is quenched with saturated $NaHCO_3$ solution and allowed to come to room temperature. The resulting suspension is filtered through a bed of celite, washing the celite pad several times with CH_2Cl_2 (total ca. 200 mL). The filtrate layers are separated and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product is chromatographed (eluent = 60% EtOAc:hexane) to give 476 mg (43%) of pure *trans*-isomer 7a together with 85 mg of a mixture of *cis*-7b and *trans* -7a isomers.

Major *trans* - isomer 7a: ^1H NMR ($CDCl_3$, d): 7.17 - 7.65 (m, 9H), 6.52 (d, J = 15.8 Hz, 1H), 6.25 (s, 1H), 6.14 (dd, J = 15.8, 7.9 Hz, 1H), 3.97 (m, 1H), 3 - 3.33 (m, 3H).

Minor *cis* - isomer 7b: ^1H NMR ($CDCl_3$, d): 7.21 - 7.52 (m, 9H), 6.62 (d, J = 15.8 Hz, 1H), 6.45 (s, 1H), 6.1 (dd, J = 15.8, 7.9 Hz, 1H), 4.46 (m, 1H), 3.7 (m, 1H), 3.02 - 3.17 (m, 1H), 2.8 - 2.93 (m, 1H).

EXAMPLE 8

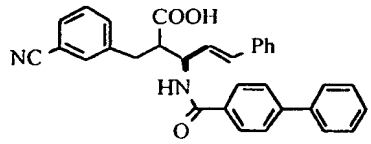
Compound 8



To a stirred solution of the trans-b-lactam 7a in dry CH_2Cl_2 under N_2 at r.t. is added triethylamine (4.04 mL; 29 mmol) dropwise. Biphenylcarbonyl chloride (5.05g; 23.2 mmol) is then added followed by DMAP (50 mg). After 30 minutes the mixture is diluted with CH_2Cl_2 and washed with 1 N HCl. The organic layer is then dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 30% EtOAc:Hexane) gave 2.19 g (81 %) of the product 8 as a solid. ^1H NMR ($CDCl_3$, δ): 8.06 (m, 2H), 7.2 - 7.75 (m, 16H), 6.67 (d, J = 15.8, Hz, 1H), 6.23 (dd, J = 15.8, 7.9 Hz, 1H), 4.63 (m, 1H), 3.46 (m, 1H), 3.1 - 3.3 (m, 2H).

EXAMPLE 9

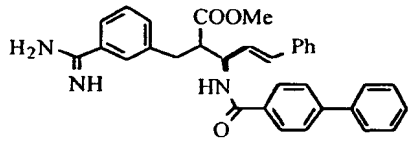
Compound 9



To a stirred solution of the b-lactam 8 (2.19 g; 4.7 mmol) in 50 mL of THF at r.t. is added 1 N NaOH solution (13.6 mL) dropwise. After 2 hours, most of the THF is removed *in vacuo* and 20 mL of 1 N HCl is added. The resulting mixture is extracted with EtOAc. The extract is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product is purified by RPHPLC (CH_3CN:water, 0.1% TFA, 40 - 100 gradient) and the fractions containing product are lyophilized to give 1.1 g (50%) of carboxylic acid 9 as a white solid. ^1H NMR ($CDCl_3$, δ): 7.18 - 7.97 (m, 18H), 6.61 (d, J = 15.8 Hz, 1H), 6.2 (dd, J = 15.8, 7.9 Hz, 1H), 5.14 (m, 1H), 3 - 3.22 (m, 3H).

EXAMPLE 10

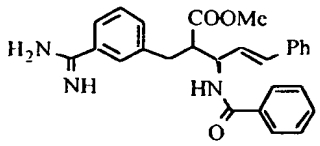
Compound 10



To a stirred solution of the carboxylic acid 9 (105 mg; 0.22 mmol) in 3 mL of dry MeOH at r.t. is added molecular sieves (ca. 50 mg). Gaseous HCl is then bubbled in for ca. 2 minutes. The mixture is then allowed to stir over night at room temperature and then concentrated under a stream of N_2. A solution of NH_3 in MeOH (3 mL of 7 N solution) is then added to the residue and the mixture refluxed for 1.5 hours, allowed to cool and the solvent removed *in vacuo*. The residue is purified by RPHPLC (CH_3CN: water: 0.1% TFA, 40-100 gradient) and the fractions containing product are lyophilized to give 73 mg (53 %) of the product 10 as a white solid. ^1H NMR (DMSO-d_6, δ): 8.7 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H), 7.75 - 7.21 (m, 14H), 6.67 (d, J = 16.1 Hz, 1H), 6.4 (dd, J = 16.1, 7.8 Hz, 1H), 4.98 (dd, J = 16.1, 7.8 Hz, 1H), 3.46 (s, 3H), 3.25 - 3.18 (m, 1H), 3.05 - 2.88 (m, 2H).

EXAMPLE 11

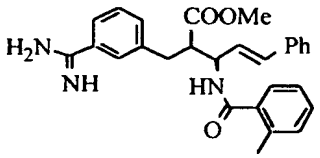
Compound 11



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 11 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (MeOH-d_4, δ): 8.61 (d, J = 11.3 Hz, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.15 - 7.67 (m, 14H), 6.67 (d, J = 15.8 Hz, 1H), 6.3 (dd, J = 15.8, 7.9 Hz, 1H), 4.98 (m, 1H), 3.55 (s, 3H), 3.27 (m, 1H), 3.1 (m, 2H).

EXAMPLE 12

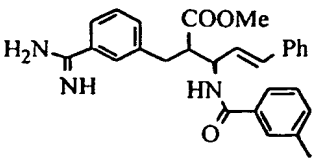
Compound 12



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. *o*-Toluoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 12 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, d): 9.3 (s, 1H), 9.15 (s, 1H), 8.7 (d, J = 7.6 Hz, 1H), 7.7 (d, J = 8 Hz, 2H), 7.6 (d, J = 9 Hz, 2H), 7.2 - 7.6 (m, 12H), 6.9 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.35 (dd, J = 15, 6 Hz, 1H), 4.9 (dd, J = 15, 6 Hz, 1H), 3.55 (s, 3H), 3.2 - 3.3 (m, 1H), 2.8 - 3 (m, 1H), 2.3 (s, 3H).

EXAMPLE 13

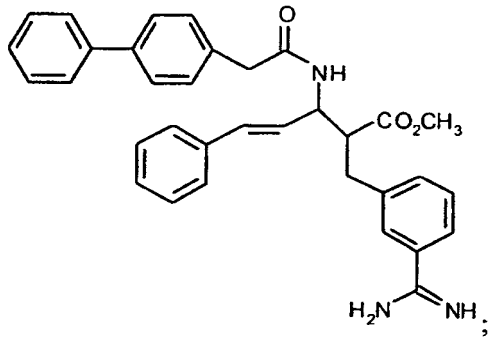
Compound 13

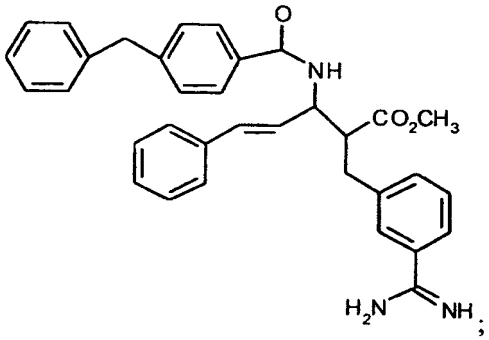


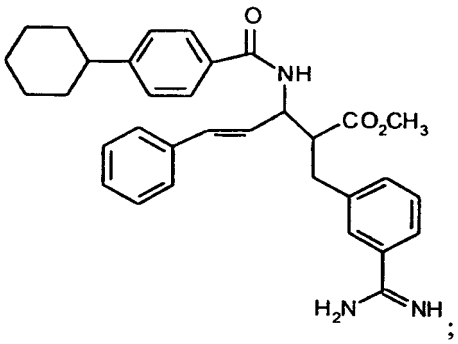
This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. *m*-Toluoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 13 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

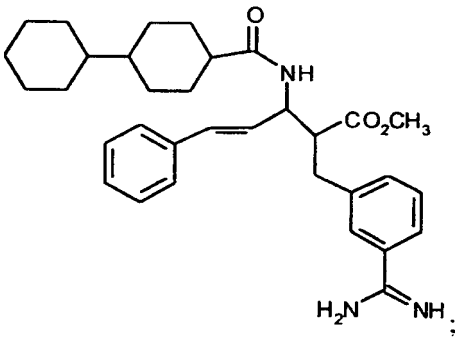
^{1}H NMR (DMSO-d6, d): 9.3 (s, 1H), 9.2 (s, 1H), 8.7 (d, J = 7.6 Hz, 1H), 7.7 (d, J = 8 Hz, 2H), 7.6 (d, J = 9 Hz, 2H), 7.2 - 7.6 (m, 12H), 6.9 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.35 (dd, J = 15, 6 Hz, 1H), 4.9 (dd, J = 16, 6 Hz, 1H), 3.6 (s, 3H), 3.2 - 3.3 (m, 1H), 2.8 - 3 (m, 1H), 2.35 (s, 3H).

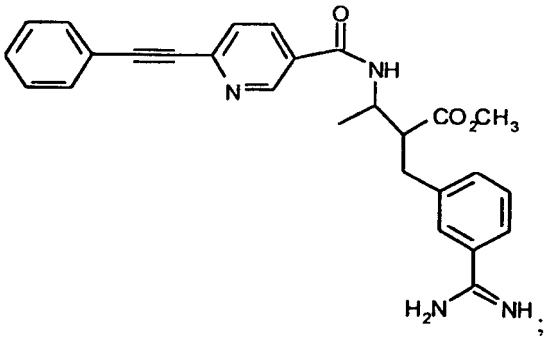
Other compounds prepared in a manner similar, using the appropriate starting material, include the following:

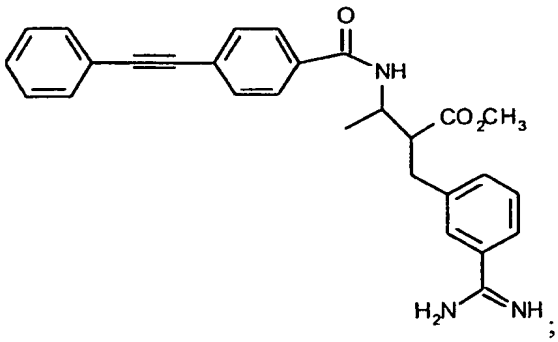


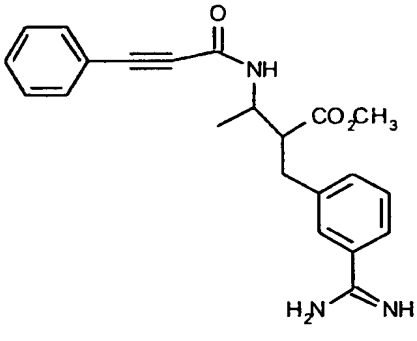




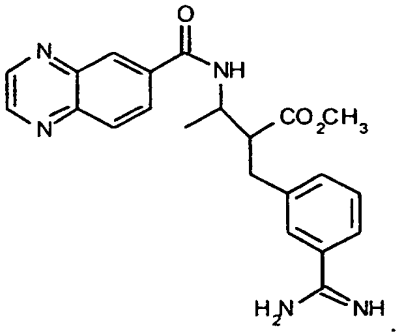






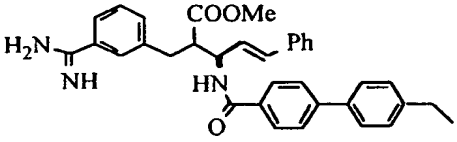


; and



EXAMPLE 14

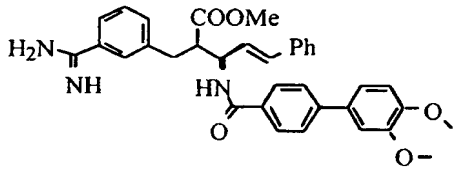
Compound 14



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 4'-Ethyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 14 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.3 (s, 1H), 9.15 (s, 1H). 8.9 (d, J = 7.6 Hz, 1H), 8.2 (d, J = 8 Hz, 2H), 8 (d, J = 9 Hz, 2H), 7.4 - 7.9 (m, 12H), 7.2 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.1 - 3.2 (m, 1H), 2.85 (q, 2H), 1.4 (t, 3H).

EXAMPLE 15

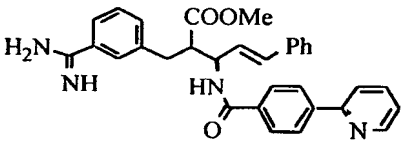
Compound 15



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 3', 4' - Dimethoxy - 4 - biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the β-lactam acylation step. The final product 15 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, d): 9.5 (s, 1H), 9.3 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.1 (d, J = 8 Hz, 2H), 7.9 (d, J = 9 Hz, 2H), 7.8 (s, 2H), 7.4 - 7.7 (m, 11H), 7.25 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.4 (dd, J = 15, 6 Hz, 1H), 4 (s, 3H), 3.9 (s, 3H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 16

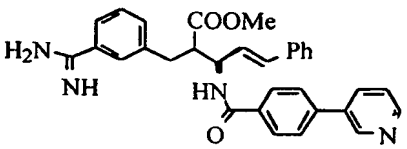
Compound 16



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 4-(2'-pyridyl)benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 16 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.5 (s, 1H), 9.3 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.8 (s, 1H), 8.4 (d, J = 8 Hz, 2H), 8.3 (d, J = 9 Hz, 1H), 8.1 (d, J = 8 Hz, 2H), 7.9 (s, 2H), 7.4 - 7.8 (m, 10H), 7.4 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 17

Compound 17

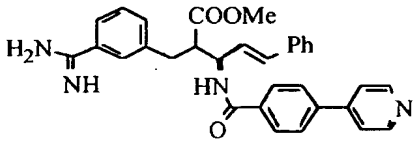


This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 4-(3'-Pyridyl)benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam

acylation step. The final product 17 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.5 (s, 1H), 9.3 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.5 (s, 1H), 8.2 (d, J = 8 Hz, 2H), 8.1 (d, J = 9 Hz, 2H), 8 (d, J = 8 Hz, 1H), 7.9 (s, 2H), 7.4 - 7.8 (m, 9H), 7.4 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 18

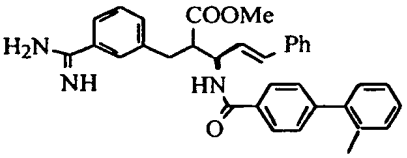
Compound 18



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 4-(4'-Pyridyl)benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 18 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.5 (s, 1H), 9.3 (s, 1H), 9 (d, J = 7.6 Hz, 1H), 8.2 (s, 4H), 7.8 (s, 2H), 7.5 - 7.8 (m, 11H), 7.4 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4 - 3.5 (m, 1H), 3.2 - 3.4 (m, 1H).

EXAMPLE 19

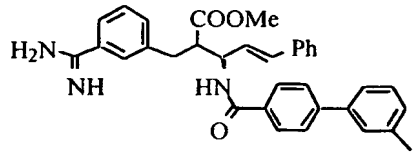
Compound 19



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 2'-Methyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 19 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.25 (s, 1H), 9.03 (s, 1H), 8.71 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8 Hz, 2H), 7.61 (d, J = 8 Hz, 2H), 7.6 - 7.12 (m, 13H), 6.67 (d, J = 15.9 Hz, 1H), 6.42 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.32 (s, 3H), 3.3 - 3.15 (m, 1H), 3.11 - 2.9 (m, 2H), 2.21 (s, 3H).

EXAMPLE 20

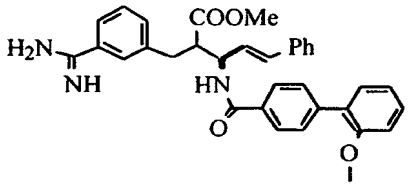
Compound 20



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 3'-Methyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 20 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.25 (s, 1H), 8.99 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.9 (d, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.68 - 7.15 (m, 13H), 6.68 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.18 (m, 1H), 3.1 - 2.9 (m, 2H), 2.36 (s, 3H).

EXAMPLE 21

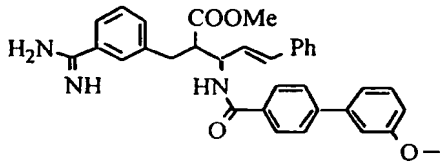
Compound 21



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 2'-Methoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 21 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.25 (s, 1H), 9.03 (s, 1H), 8.76 (δ, J = 8.7 Hz, 1H), 7.83 (d, J = 9.5 Hz, 2H), 7.65 - 6.95 (m, 15H), 6.64 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 4.99 (dd, J = 16, 7.9 Hz, 1H), 3.75 (s, 3H), 3.46 (s, 3H), 3.3 - 3.17 (m, 1H), 3.1 - 2.9 (m, 2H).

EXAMPLE 22

Compound 22

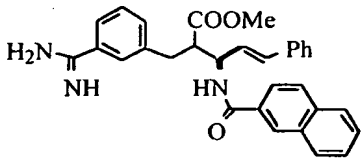


This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4 3'-Methoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the

b-lactam acylation step. The final product 22 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.23 (s, 1H), 8.96 (s, 1H), 8.69 (d, J = 8.7 Hz, 1H), 7.9 (d, J = 9.6 Hz, 2H), 7.68 - 7.18 (m, 12H), 6.96 (dd, J = 9.6, 2 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.9 Hz, 1H), 3.81 (s, 3H), 3.47 (s, 3H), 3.28 - 3.17 (m, 1H), 3.08 - 2.86 (m, 2H).

EXAMPLE 23

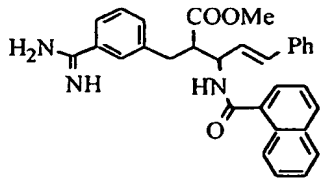
Compound 23



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 2-Naphthylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 23 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.24 (s, 1H), 9.02 (s, 1H), 8.83 (d, J = 8.6 Hz, 1H), 8.4 (s, 1H), 8.08 - 7.85 (m, 4H), 7.68 - 7.2 (m, 12H), 6.68 (d, J = 15.8 Hz, 1H), 6.43 (dd, J = 15.8, 7.8 Hz, 1H), 5.03 (dd, J = 15.8, 7.8 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.2 (m, 1H), 3.13 - 2.95 (m, 2H).

EXAMPLE 24

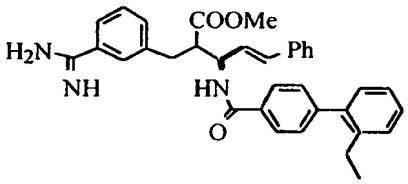
Compound 24



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 1-Naphthylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 24 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.27 (s, 1H), 9.11 (s, 1H), 8.88 (d, J = 8.67 Hz, 1H), 8.18 - 8.07 (m, 1H), 8.05 - 7.9 (m, 2H), 7.7 - 7.2 (m, 13H), 6.73 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 5.07 (dd, J = 16, 7.9 Hz, 1H), 3.52 (s, 3H), 3.28 - 3.17 (m, 1H), 3.12 - 2.95 (m, 2H).

EXAMPLE 25

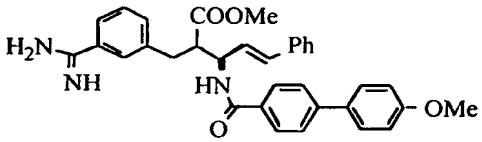
Compound 25



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 3'-Ethyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 25 is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized. ^{1}H NMR (DMSO-d_6, δ): 9.25 (s, 1H), 9.05 (s, 1H), 8.68 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 7.62 (m, 2H), 7.55 - 7.15 (m, 11H), 6.66 (d, J = 16 Hz, 1H), 6.4 (dd, J = 16, 7.8 Hz, 1H), 4.96 (dd, J = 16, 7.8 Hz, 1H), 3.47 (s, 3H), 3.3 - 3.18 (m, 1H), 3.1 - 2.88 (m, 2H), 2.67 (q, J = 8.5 Hz, 2H), 1.22 (t, J = 8.5 Hz, 3H).

EXAMPLE 26

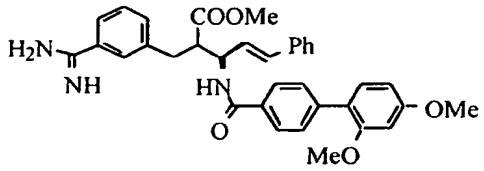
Compound 26



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 4'-Methoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 26 is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized. ^{1}H NMR (DMSO-d_6, δ): 9.23 (s, 1H), 8.96 (s, 1H), 8.66 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 9.1 Hz, 2H), 7.72 - 7.22 (m, 11H), 7.03 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 16.1 Hz, 1H), 6.4 (dd, J = 16.1, 7.9 Hz, 1H), 4.97 (dd, J = 16.1, 7.9 Hz, 1H), 3.77 (s, 3H), 3.46 (s, 3H), 3.28 - 3.15 (m, 1H), 3.08 - 2.88 (m, 2H).

EXAMPLE 27

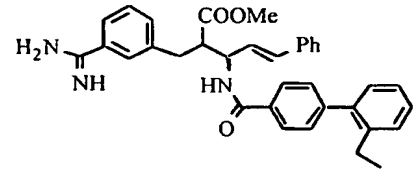
Compound 27



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 2', 4'- Dimethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 27 is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized. ^{1}H NMR (DMSO-d_6, δ): 9.23 (s, 1H), 9.07 (s, 1H), 8.63 (d, J = 9 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.68 - 7.15 (m, 14H), 6.72 - 6.52 (m, 1H), 6.45 - 6.3 (m, 1H), 5.04 - 4.9 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.51 (s, 3H), 3.21 - 3.15 (m, 1H), 3.08 - 2.85 (m, 2H).

EXAMPLE 28

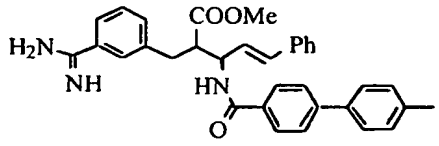
Compound 28



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 2'-Ethyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 28 is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized. ^{1}H NMR (DMSO-d_6, δ): 9.25 (s, 1H), 8.92 (s, 1H), 8.69 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 9 Hz, 2H), 7.68 - 7.08 (m, 15H), 6.65 (d, J = 15.9 Hz, 1H), 6.38 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.18 (m, 1H), 2.52 (q, J = 9.6 Hz, 2H), 0.98 (t, J = 9.6 Hz, 3H).

EXAMPLE 29

Compound 29

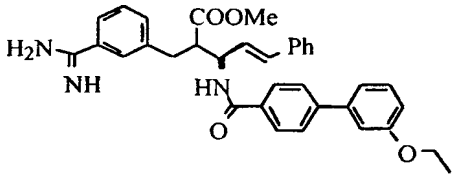


This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 4'-Methyl-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the

b-lactam acylation step. The final product 29 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.22 (s, 1H), 8.91 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 9 Hz, 2H), 7.75 (d, J = 9 Hz, 2H), 7.65 - 7.2 (m, 13H), 6.65 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.99 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28 - 3.18 (m, 1H), 3.08 - 2.88 (m, 2H), 2.35 (s, 3H).

EXAMPLE 30

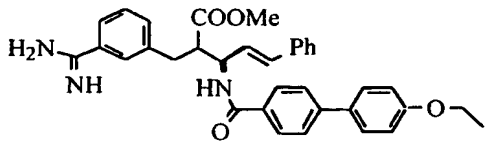
Compound 30



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 3'-Ethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 30 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.22 (s, 1H), 9.05 (s, 1H), 8.7 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 7.68 - 7.12 (m, 12H), 6.98 - 6.85 (m, 1H), 6.67 (d, J = 16 Hz, 1H), 6.4 (dd, J = 16, 7.8 Hz, 1H), 5.01 (dd, J = 16, 7.8 Hz, 1H), 4.08 (q, J = 7.5 Hz, 2H), 3.45 (s, 3H), 3.25 - 3.15 (m, 1H), 3.08 - 2.89 (m, 2H), 1.32 (t, J = 7.5 Hz, 2H).

EXAMPLE 31

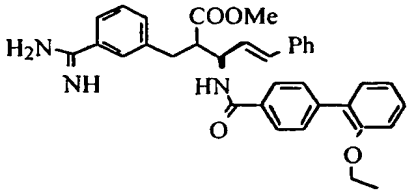
Compound 31



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 4'-Ethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the β-lactam acylation step. The final product 31 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.26 (s, 1H), 9.02 (s, 1H), 8.64 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 9 Hz, 2H), 7.72 (d, J = 9 Hz, 2H), 7.7 - 7.22 (m, 11H), 7.01 (d, J = 10.4 Hz, 2H), 6.64 (d, J = 15.9 Hz, 1H), 6.38 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.8 Hz, 1H), 4.06 (q, J = 8.2 Hz, 2H), 3.45 (s, 3H), 3.3 - 3.18 (m, 1H), 3.08 - 2.85 (m, 2H), 1.32 (t, J = 8.2 Hz, 3H).

EXAMPLE 32

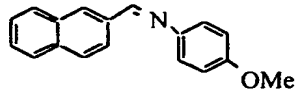
Compound 32



This compound is prepared in a manner similar to compound 10 above starting from imine 5 and thioester 4. 2'-Ethoxy-4-biphenylcarbonyl chloride is substituted for 4-biphenylcarbonyl chloride in the β-lactam acylation step. The final product 32 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^{1}H NMR (DMSO-d_6, δ): 9.24 (s, 1H), 9.11 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 9 Hz, 2H), 7.6 (d, J = 9 Hz, 2H), 7.59 - 6.95 (m, 13H), 6.65 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.8 Hz, 1H), 4.03 (q, J = 8.1 Hz, 2H), 3.47 (s, 3H), 3.28 - 3.18 (m, 1H), 3.1 - 2.88 (m, 2H), 1.24 (t, J = 8.1 Hz, 3H).

EXAMPLE 33

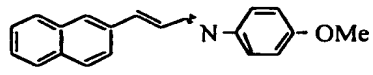
Compound 33



To a stirred solution of 2-Naphthaldehyde (20 g; 0.13 mol) in 200 mL of CH_2Cl_2 at room temp. is added p-anisidine (15.8 g; 0.13 mol) followed by anhydrous magnesium sulfate (16.9 g; 0.14 mol). After 3.5 hours, the mixture is filtered and the filtrate concentrated *in vacuo* to give 31.5 g (92%) of the imine 33. ^{1}H NMR ($CDCl_3$, δ): 8.64 (s, 1H), 8.19 (m, 2H), 7.78 - 7.98 (m, 3H), 7.43 - 7.56 (m, 2H), 7.32 (m, 2H), 6.96 (m, 2H), 3.83 (s, 3H).

EXAMPLE 34

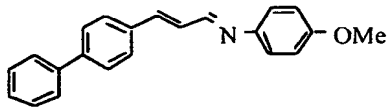
Compound 34



Prepared using *trans* - 3- (2'-naphthyl)acrolein, p-anisidine and anhydrous magnesium sulfate as described for compound 33 above. ^{1}H NMR ($CDCl_3$, δ): 8.35 (d, J = 9 Hz, 1H), 7.78 - 7.9 (m, 4H), 7.72 (m, 1H), 7.5 (m, 2H), 7.25 (m, 4H), 6.93 (m, 2H), 3.82 (s, 3H).

EXAMPLE 35

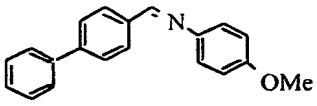
Compound 35



Prepared using *trans*- 3 - (4'-biphenyl)acrolein, p-anisidine and anhydrous magnesium sulfate as described for compound 33 above. ^{1}H NMR ($CDCl_3$, δ): 8.33 (d, J = 9 Hz, 1H), 7.2 - 7.68 (m, 13H), 6.9 (m, 2H), 3.82 (s, 3H).

EXAMPLE 36

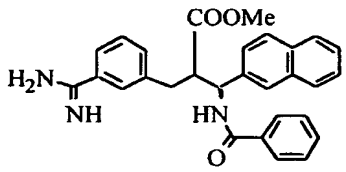
Compound 36



Prepared using 4-biphenylcarboxaldehyde, p-anisidine and anhydrous magnesium sulfate as described for compound 33 above. ^{1}H NMR ($CDCl_3$, δ): 8.52 (s, 1H), 7.97 (m, 2H), 7.62 - 7.73 (m, 4H), 7.35 - 7.52 (m, 3H), 7.27 (m, 2H), 6.95 (m, 2H), 3.85 (s, 3H).

EXAMPLE 37

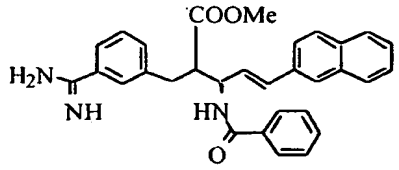
Compound 37



This compound is prepared in a manner similar to compound 10 starting from imine 33 and thioester 4. Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 37 is purified by reverse phase HPLC (CH_3CN:H_2O, 0.1% TFA) and lyophilized. ^{1}H NMR (MeOH-d_4, δ): 9.01 (d, J = 9.4 Hz, 1H), 7.77 - 7.98 (m, 6H), 7.43 - 7.67 (m, 9H), 5.53 (m, 1H), 3.56 (m, 1H), 3.54 (s, 3H), 3.1 (m, 1H), 2.81 (m, 1H).

EXAMPLE 38

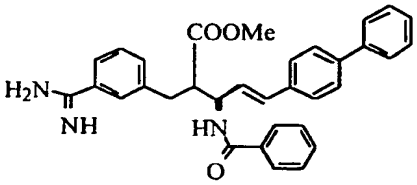
Compound 38



This compound is prepared in a manner similar to compound 10 starting from imine 34 and thioester 4. Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 38 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.27 (s, 2H), 9.1 (s, 2H), 8.72 (d, 1H), 7.4 - 7.95 (m, 16H), 6.86 (d, J = 18 Hz, 1H), 6.54 (dd, J = 10, 6 Hz, 1H), 5.03 (m, 1H), 3.48 (s, 3H), 3.32 (m, 1H), 3.04 (m, 2H).

EXAMPLE 39

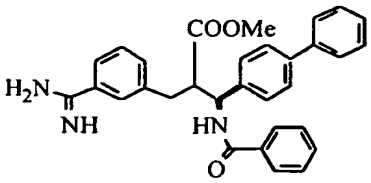
Compound 39



This compound is prepared in a manner similar to compound 10 starting from imine 35 and thioester 4. Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 39 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized. ^1H NMR (DMSO-d_6, δ): 9.25 (s, 2H), 9.11 (s, 2H), 8,74 (d, 1H), 7.30 - 8 (m, 22H), 6.23 (d, J = 18 Hz, 1H), 6.47 (dd, J = 18, 6 Hz, 1H), 5.04 (m, 1H), 3.49 (s, 3H), 3.3 (m, 1H), 3.03 (m, 2H).

EXAMPLE 40

Compound 40

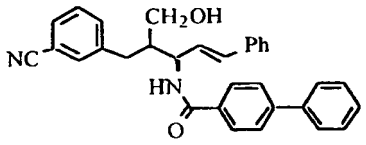


This compound is prepared in a manner similar to compound 10 starting from imine 36 and thioester 4. Benzoyl chloride is substituted for 4-biphenylcarbonyl chloride in the b-lactam acylation step. The final product 40 is purified by reverse phase HPLC ($CH_3CN:H_2O$, 0.1% TFA) and lyophilized.

^{1}H NMR (DMSO-d_6, δ): 9.23 (s, 2H), 9.05 (s, 2H), 8.97 (s, 2H), 7.28 - 7.8 (m, 18H), 5.35 (t, 1H), 3.42 (s, 3H), 3.31 (m, 1H), 2.89 (dd, 1H), 2.6 (dd, 1H).

EXAMPLE 41

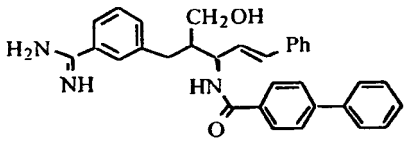
Compound 41



To a stirring solution of the carboxylic acid 9 (980 mg; 2 mmol) and triethylamine (0.44 mL; 3.2 mmol) in dry THF under N_2 at 0°C is added i-butylchloroformate (0.39 mL; 3 mmol) dropwise. After 15 minutes, a solution of sodium borohydride (153 mg; 4 mmol in 5 mL water) is added dropwise. The mixture is allowed to warm up to room temperature. After 1 hour, most of the THF is removed *in vacuo*. Water is then added and the mixture extracted with ethyl acetate. The combined extracts are dried ($MgSO_4$), filtered and concentrated. The crude product is purified by chromatography (eluent = 35% EtOAc:Hexane) to give 720 mg (76%) of the alcohol 41. ^{1}H NMR ($CDCl_3$, δ): 7.92 (d, J = 9 Hz, 2H), 7.2 - 7.72 (m, 16H), 6.67 (d, J = 15.5 Hz, 1H), 6.27 (dd, J = 15.5, 7.8 Hz, 1H), 4.94 (m, 1H), 3.88 (m, 1H), 3.5 (m, 1H), 3.12 (m, 1H), 2.82 - 3.03 (m, 2H), 1.95 (m, 1H).

EXAMPLE 42

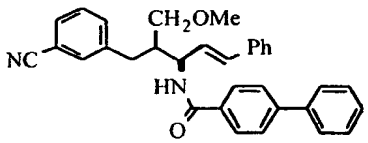
Compound 42



To a stirred solution of the alcohol 41 (106 mg; 0.22 mmol) in 3 mL of dry MeOH at r.t. is added molecular sieves (ca. 50 mg). Gaseous HCl is then bubbled in for ca. 2 minutes The mixture is then allowed to stir over night at room temperature and then concentrated under a stream of N_2. A solution of NH_3 in MeOH (3 mL of 7 N solution) is then added to the residue and the mixture refluxed for 1.5 hour, allowed to cool and the solvent removed *in vacuo*. The residue is purified by RPHPLC (CH_3CN: water: 0.1% TFA, 40-100 gradient) and the fractions containing product are lyophilized to give 29 mg (22 %) of the product 42 as the trifluoroacetate salt.

EXAMPLE 43

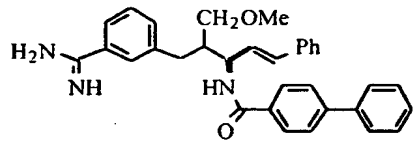
Compound 43



To a stirring solution of the alcohol compound (88 mg: 0.2 mmol) in 2 mL of 2:1 THF:DMF under N_2 at 0°C is added NaH (15 mg of 60% dispersion; 0.4 mmol). After 15 minutes, methyl iodide (0.02 mL; 0.3 mmol) is added and the mixture allowed to warm to room temperature. After 2 hours, the mixture is quenched with saturated $NaHCO_3$ solution. Most of the THF is removed *in vacuo* and the residue diluted with water and extracted with CH_2Cl_2. The combined extracts are dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 35% EtOAc:Hexane) to give 21 mg (23%) of the product 43 together with 34 mg of recovered alcohol 41. ^1H NMR ($CDCl_3$, δ): 7.93 (d, J = 9.3 Hz, 2H), 7.15 - 7.83 (m, 16H), 6.57 (d, J = 15.8 Hz, 1H), 6.22 (dd, J = 15.8, 6.8 Hz, 1H), 5 (m, 1H), 3.75 (m, 1H), 3.42 (s, 3H), 3.27 (m, 1H), 2.87 - 3.03 (m, 2H), 2.12 (m, 1H).

EXAMPLE 44

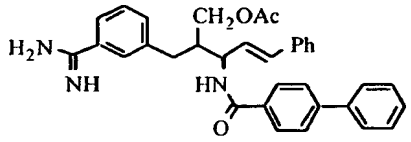
Compound 44



Into a stirring solution of compound 43 (20 mg; 0.04 mmol) in 1.5 mL of 2:1 pyridine:Et3N is bubbled H_2S for about 1 minute. The mixture is allowed to stir overnight at room temperature and then concentrated under a stream of N_2 and then taken up into 2 mL of CH_2Cl_2. Methyl iodide (1 mL) is added and the mixture refluxed for 1 hour. The solvent is then removed *in vacuo*, the residue taken up into 2 mL of MeOH and NH_4OAc (30 mg) is added. The resulting mixture is refluxed for 1 hour and then allowed to cool. The solvent is then removed *in vacuo* and the residue is purified by RPHPLC (CH_3CN:H_2O, 0.1% TFA, 40 to 100% CH_3CN gradient) and the fractions containing product are lyophilized to give 13 mg (51%) of product 44 as the trifluoroacetate salt. ^1H NMR (MeOH-d4, δ): 8.47 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8 Hz, 2H), 7.78 (d, J = 8 Hz, 2H), 7.17 - 7.73 (m, 14 H), 6.55 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 15.8, 7.9 Hz, 1H), 4.77 (m, 1H), 3.7 (dd, J = 9.5, 3.1 Hz, 1H), 3.47 (dd, J = 9.5, 3.1 Hz, 1H), 3 (d, J = 7.9 Hz, 2H), 2.35 (m, 1H).

EXAMPLE 45

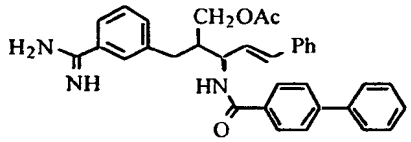
Compound 45



A mixture of alcohol 41 (480 mg; 1 mmol), pyridine (0.40 mL; 4.9 mmol) and acetic anhydride (0.12 mL; 1.2 mmol) is stirred overnight at room temperature. The next day, 3 drops of pyridine and acetic anhydride are added. The next day, the reaction is not complete and so 4 mg of DMAP is added. After 1 hour, the reaction is complete by tlc. The mixture is diluted with CH_2Cl_2 and washed with 0.1 N HCl solution. The organic layer is dried ($MgSO_4$), filtered and concentrated to give 520 mg of 45. ^1H NMR ($CDCl_3$, δ): 7.98 (d, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.17 - 7.58 (m, 12H), 6.94 (d, 1H), 6.55 (d, J = 18 Hz, 1H), 6.21 (dd, J = 18, 5 Hz, 1H), 5.1 (m, 1H), 4.38 (m, 1H), 4.08 (m, 1H), 2.68 - 2.97 (m, 2H), 2.51 (m, 1H).

EXAMPLE 46

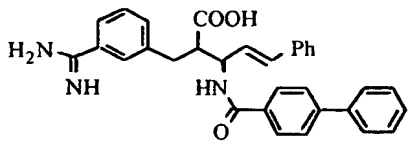
Compound 46



Compound 45 is converted to the corresponding amidine 46 using the hydrogen sulfide /methyl iodide: ammonium acetate sequence described for the conversion of 43 to 44. The product 46 is purified by RPHPLC and isolated as its trifluoroacetate salt. ^1H NMR (DMSO-d_6, δ): 9.31 (s, 2H), 8.97 (s, 2H), 8.7 (d, 1H), 7.18 - 8 (m, 18H), 6.6 (d, J = 18 Hz, 1H), 6.40 (dd, J = 18, 6 Hz, 1H), 4.83 (m, 1H), 4.02 (m, 1H), 3.84 (m, 2H), 2.95 (m, 1H), 2.57 (m, 1H), 1.93 (s, 3H).

EXAMPLE 47

Compound 47

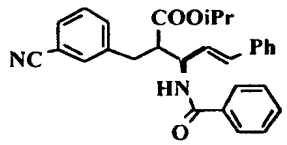


Carboxylic acid 9 is converted to its corresponding amidine 47 using the hydrogen sulfide: methyl iodide: ammonium acetate sequence described for the conversion of 43 to 44. The product 47 is isolated by RPHPLC as its trifluoroacetate salt. ^1H NMR (MeOH-d_4, δ): 8 (d, J = 9 Hz, 2H), 7.82 (d, J

= 9 Hz, 2H), 7.22 - 7.77 (m, 14H), 6.73 (d, J = 15.8 Hz, 1H), 6.4 (dd, J = 15.8, 7.9 Hz, 1H), 4.95 (m, 1H), 3.08 - 3.45 (m, 3H).

EXAMPLE 49

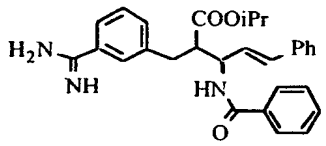
Compound 49



To a stirring solution of the carboxylic acid 48 (120 mg; 0.29 mmol) in 5 mL of dry CH_2Cl_2 under N_2 at room temperature is added triethylamine (0.05 mL; 0.38 mmol). iso-propyl chloroformate (0.38 mL of 1 M solution in toluene) is added dropwise. After 30 minutes, DMAP (18 mg; 0.15 mmol) is added and the mixture allowed to further stir for 1.5 hours at room temperature. The mixture is then diluted with CH_2Cl_2 and washed with 1 N HCl. The organic layer is then dried ($MgSO_4$), filtered and concentrated. The crude product is chromatographed (eluent = 40% EtOAc:Hexane to give 44 mg (33 %) of the corresponding isopropyl ester. This compound is then converted to the corresponding amidine 49 via the hydrogen sulfide: methyl iodide: ammonium acetate procedure as described for the conversion of 43 to 44. The product 49 is purified by RPHPLC and isolated as its trifluoroacetate salt. ^{1}H NMR (MeOH-d4, δ): 8.6 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.16 - 7.7 (m, 12H), 6.69 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8, 7.9 Hz, 1H), 4.98 (m, 1H), 4.85 (m, 1H), 3.23 (m, 1H), 3.08 (m, 2H), 1.07 (d, J = 6 Hz, 3H), 0.97 (d, J = 6 Hz, 3H).

EXAMPLE 50

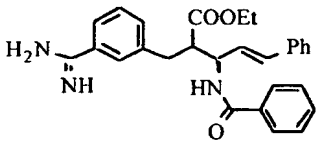
Compound 50



This compound is prepared by conversion of 48 to the corresponding amidine using the hydrogen sulfide: methyl iodide: ammonium acetate sequence described for the conversion of 43 to 44. The product 50 is purified by RPHPLC and isolated as its trifluoroacetate salt. ^{1}H NMR (MeOH-d4, δ): 8.6 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.16 - 7.7 (m, 12H), 6.69 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8, 7.9 Hz, 1H), 4.98 (m, 1H), 4.85 (m, 1H), 3.23 (m, 1H), 3.08 (m, 2H), 1.07 (d, J = 6 Hz, 3H), 0.97 (d, J = 6 Hz, 3H).

EXAMPLE 51

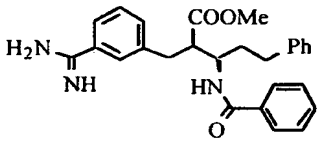
Compound 51



Into a stirred solution of the carboxylic acid 50 (96 mg; 0.18 mmol) in 3 mL of EtOH at room temperature is bubbled HCl for ca. 3 minutes. The mixture is allowed to stir for 7 hours at room temperature and then stored in the refrigerator (0°C) over the weekend. The solvent is then removed *in vacuo* and the residue purified by RPHPLC. The product 51 is isolated as its trifluoroacetate salt. ^{1}H NMR (MeOH-d4, δ): 8.63 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8 Hz, 2H), 7.16 - 7.68 (m, 12H), 6.68 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8, 7.9 Hz, 1H), 5 (m, 1H), 4.02 (q, 2H), 3.25 (m, 1H), 3.07 (d, J = 7.9 Hz, 2H), 1.05 (t, 3H).

EXAMPLE 52

Compound 52



A mixture of compound and 10% Pd/C (25 mg) in EtOAc (2 mL): EtOH (5 mL) is hydrogenated under 45 PSI H_2 for 19 hours at room temperature. The mixture is then filtered through a bed of celite and the filtrate concentrated. The crude product is purified by RPHPLC (CH_3CN:water: 0.1 % TFA, 10 - 100% CH_3CN gradient) and the fractions containing product are lyophilized to give 21 mg of 52. ^{1}H NMR (MeOH-d4, δ): 8.27 (d, J = 9.3 Hz, 1H), 7.83 (m, 2H), 7.43 - 7.65 (m, 7H), 7.09 - 7.27 (m, 5H), 4.35 (m, 1H), 3.58 (s, 3H), 2.95 - 3.15 (m, 3H), 2.54 - 2.75 (m, 2H), 1.93 (m, 2H).

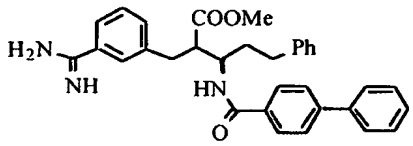
Resolution of Compound 10

Racemic compound 10 (ca. 650 mg, single diastereomer with the presumed syn-stereochemistry shown) is resolved into its two enantiomers 53 (late eluting isomer) and 54 (early eluting isomer) using preparative HPLC (Chiralpak AD column, 50 mm ID x 500 mm, 15 microns). The mobile phase is heptane (A) with 0.1% TFA and i-propanol (B) with 0.1% TFA, isocratic 20% A, 80% B (Flow = 200 mL: minute). The late eluting isomer is isolated by concentration *in vacuo*. The yield is 180 mg. The %ee enantiomer 53 is found to be 100% by analytical HPLC (Chiralpak AD). The ^{1}H NMR spectra for 53 and 54 are identical. ^{1}H NMR (DMSO-d6, δ): 8.7 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 9 Hz, 2H), 7.78 (d,

J = 9 Hz, 2H), 7.75 - 7.21 (m, 14H), 6.67 (d, J = 16.1 Hz, 1H), 6.4 (dd, J = 16.1, 7.8 Hz, 1H), 4.98 (dd, J = 16.1, 7.8 Hz, 1H), 3.46 (s, 3H), 3.25 - 3.18 (m, 1H), 3.05 - 2.88 (m, 2H).

EXAMPLE 55

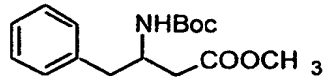
Compound 55



The hydrogenation of compound 53 (late eluting enantiomer) is carried out as for compound 52 above except ethyl acetate is omitted. The product is purified by RPHPLC (CH_3CN:water: 0.1 % TFA, 40 - 100% CH_3CN) and the product 55 is isolated as the trifluoroacetate salt. ^1H NMR (MeOH-d_4, δ): 8.3 (d, J = 9.3 Hz, 1H), 7.84 (m, 2H), 7.07 - 7.8 (m, 16H), 4.37 (m, 1H), 3.6 (s, 3H), 2.97 - 3.17 (m, 3H), 2.57 - 2.77 (m, 2H), 1.95 (m, 2H).

EXAMPLE 56

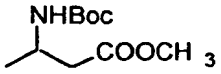
Compound 56



To a solution of N-a-Boc-D-Phenylalanine (38 mmol) in 80 mL of dry tetrahydrofuran is added N-methyl morpholine (38 mmol) in a single portion, followed by isobutyl chloroformate (38 mmol) in a similar fashion, at -20°C. The reaction mixture is stirred for 10 minutes at -20°C and filtered into a preformed ethereal solution of diazomethane (~70 mmol) at 0°C. The resulting solution is allowed to stand at 0°C for 20 minutes. Excess diazomethane is decomposed by the dropwise addition of glacial acetic acid and solvents are removed *in vacuo*. The resulting oil is dissolved in 150 mL of dry methanol. A solution of silver benzoate (8 mmol) in 17 mL of triethylamine is slowly added with stirring, at room temperature. The resulting black reaction mixture is stirred for 45 minutes at room temperature. Methanol is removed *in vacuo* and the residue taken up in 700 mL of ethyl acetate. The mixture is filtered through celite and washed sequentially with saturated sodium bicarbonate (3X150 mL), water (1X150 mL), 1N potassium bisulfate (3x150 mL) and brine (1X150 mL). The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (3:1 hexanes:ethyl acetate).

EXAMPLE 57

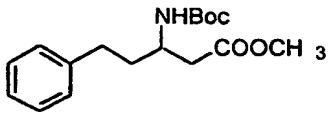
Compound 57



Compound 57 is prepared using the procedure described for Compound 56, substituting N-a-Boc-D-alanine.

EXAMPLE 58

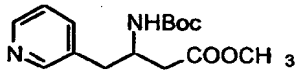
Compound 58



Compound 58 is prepared using the procedure described for Compound 56, substituting N a -Boc-D-homophenylalanine.

EXAMPLE 59

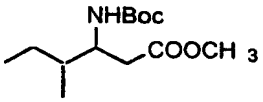
Compound 59



Compound 59 is prepared using the procedure described for Compound 56, substituting N-a-Boc-D-3-pyridylalanine.

EXAMPLE 60

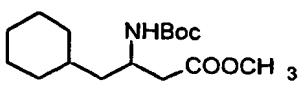
Compound 60



Compound 60 is prepared using the procedure described for 56, substituting N-a -Boc-D-isoleucine.

EXAMPLE 61

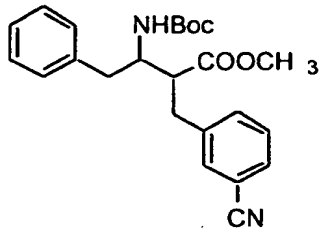
Compound 61



Compound 61 is prepared using the procedure described for Compound 56, substituting N-a -Boc-D-cyclohexylalanine.

EXAMPLE 62

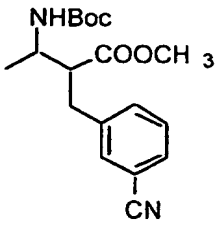
Compound 62



A solution of Compound 56 (11 mmol) in 70 mL of dry tetrahydrofuran is cooled to -78°C and a solution of lithium hexamethyldisilazane in tetrahydrofuran (33 mmol) is added via syringe at such a rate that the temperature did not rise above -60°C. The reaction mixture is warmed to -25°C over 40 minutes and recooled to -78°C. A solution of 3-cyanobenzyl bromide (27 mmol) in 20 mL of tetrahydrofuran is added via syringe at such a rate that the temperature did not rise above -60°C. The reaction mixture is allowed to come to room temperature and stirred at room temperature for 1 hour. 125 mL of saturated sodium bicarbonate is added and tetrahydrofuran is removed *in vacuo*. The remaining material is partitioned between 500 mL of ethyl acetate and 150 mL of saturated sodium bicarbonate. The organic phase is further washed with saturated sodium bicarbonate (2x100 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo. The residue is triturated with 40 mL of 4:1 hexanes:ethyl acetate. The solid material is filtered off and discarded. The filtrate, containing the desired product, is concentrated *in vacuo*.

EXAMPLE 63

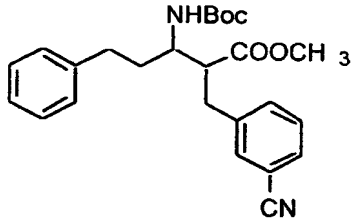
Compound 63



Compound 63 is prepared following the method described for Compound 62, substituting the product obtained in Example 57.

EXAMPLE 64

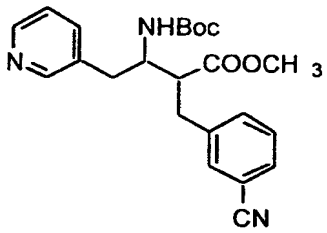
Compound 64



Compound 64 is prepared following the method described for Compound 62, substituting the product obtained in Example 58.

EXAMPLE 65

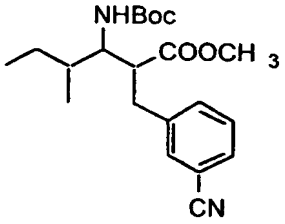
Compound 65



Compound 65 is prepared following the method described for Compound 62, substituting the product obtained in Example 59.

EXAMPLE 66

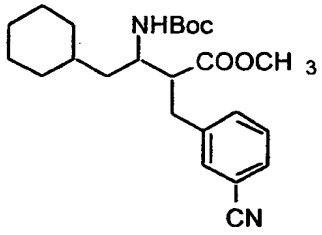
Compound 66



Compound 66 is prepared following the method described for Compound 62, substituting the product obtained in Example 60.

EXAMPLE 67

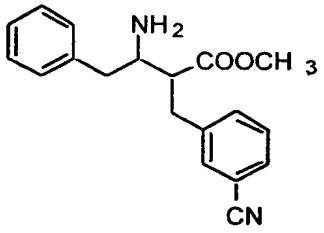
Compound 67



Compound 67 is prepared following the method described for Compound 62, substituting the product obtained in Example 61.

EXAMPLE 68

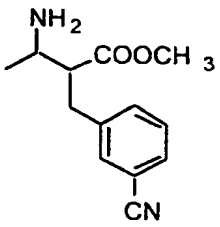
Compound 68



To a solution of Compound 62 (5 mmol) in 60 mL of methylene chloride is added 20 mL of trifluoroacetic acid, dropwise at 0°C. The resulting solution is stirred for 2 hours at 0°C. Solvents are removed *in vacuo* and the residue purified by reverse phase HPLC using a gradient of 30% to 70% acetonitrile in water containing 0.1% trifluoroacetic acid. Acetonitrile is removed in vacuo and the remaining material partitioned between saturated sodium bicarbonate and ethyl acetate. The aqueous layer is extracted twice with ethyl acetate and the combined organic layers are dried over magnesium sulfate, filtered, and concentrated in vacuo.

EXAMPLE 69

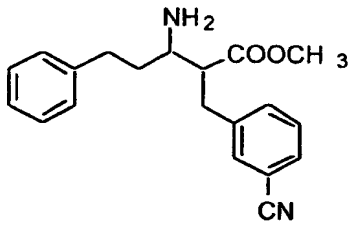
Compound 69



Compound 69 is prepared according to the method described in Example 68, substituting the product obtained in Example 63.

EXAMPLE 70

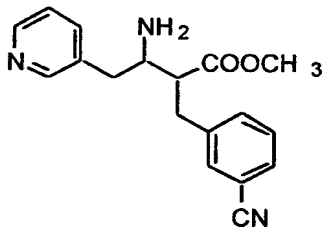
Compound 70



Compound 70 is prepared according to the method described in Example 68, substituting the product obtained in Example 64.

EXAMPLE 71

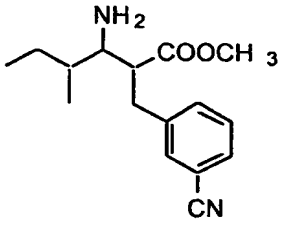
Compound 71



Compound 71 is prepared according to the method described in Example 68, substituting the product obtained in Example 65.

EXAMPLE 72

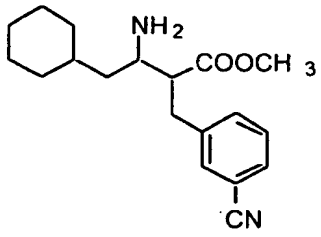
Compound 72



Compound 72 is prepared according to the method described in Example 68, substituting the product obtained in Example 66.

EXAMPLE 73

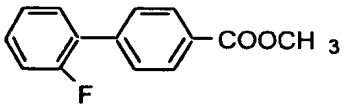
Compound 73



Compound 73 is prepared according to the method described in Example 68, substituting the product obtained in Example 67.

EXAMPLE 74

Compound 74

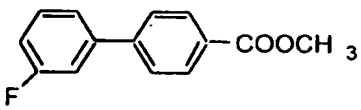


Solution (A): To a solution of 11.8 mL of n-butyl lithium in hexanes (19 mmol) in 13 mL of tetrahydrofuran is added a solution of 1-bromo-2-fluorobenzene (19 mmol) in 2 mL of tetrahydrofuran, dropwise via syringe at -78°C. Stirring at -78 °C is continued for 1 hour. A solution of zinc chloride (19 mmol) in 38 mL of tetrahydrofuran is added over 2 minutes at -78°C. The resulting solution is allowed to come to room temperature over 40 minutes.

Solution (B): To a solution of bis(triphenylphosphine) palladium dichloride (1 mmol) in 11 mL of tetrahydrofuran is added diisobutyl aluminum hydride (1 mmol) as a solution in hexanes, at room temperature, followed by methyl iodobenzoate(16 mmol) in a single portion at room temperature. Solution (A) is added to solution (B) and the reaction mixture allowed to stir at room temperature overnight. The reaction mixture is diluted with 300 mL of diethyl ether and washed with 1N hydrochloric acid (3x75 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, and concentrated in vacuo.

EXAMPLE 75

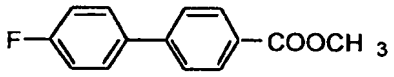
Compound 75



Compound 75 is prepared according to the method described for Compound 74, substituting 1-bromo-3-fluorobenzene in the preparation of Solution (A).

EXAMPLE 76

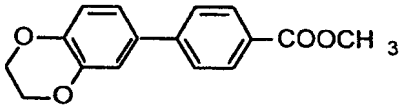
Compound 76



Compound 76 is prepared according to the method described for Compound 74, substituting 1-bromo-4-fluorobenzene in the preparation of Solution (A).

EXAMPLE 77

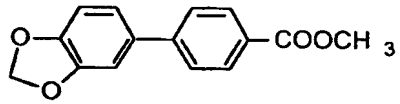
Compound 77



Compound 77 is prepared according to the method described in EXAMPLE 74, substituting 3,4-ethylenedioxy bromobenzene in the preparation of Solution (A).

EXAMPLE 78

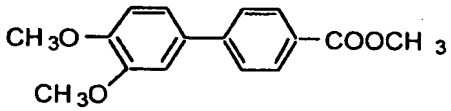
Compound 78



Compound 78 is prepared according to the method described in EXAMPLE 74, substituting 3,4-methylenedioxy bromobenzene in the preparation of Solution (A).

EXAMPLE 79

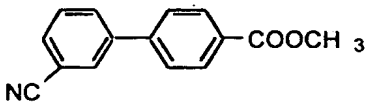
Compound 79



Compound 79 is prepared according to the method described in Example 74, substituting 3,4-dimethoxy bromobenzene in the preparation of Solution (A).

EXAMPLE 80

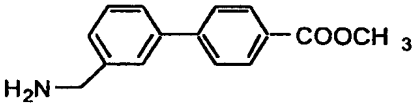
Compound 80



Compound 80 is prepared according to the method described in Example 74, substituting 3-cyano bromobenzene in the preparation of Solution (A).

EXAMPLE 81

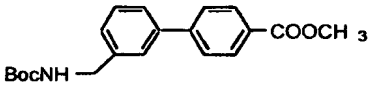
Compound 81



Ammonia gas is bubbled into a suspension of Compound 80 (24 mmol) in 200 mL of methanol for five minutes. To the resulting solution is added rhodium on alumina (5 g) and the suspension is shaken under a positive pressure of hydrogen for 36 hours. Catalyst is filtered off and methanol is removed in vacuo to give an oil which is triturated with ether and filtered.

EXAMPLE 82

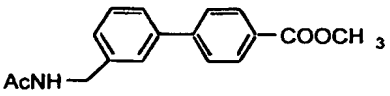
Compound 82



A solution of Compound 81 (15.4 mmol), triethylamine (17 mmol), di-tert-butyl dicarbonate (15.4 mmol), and 4-dimethylaminopyridine (1.5 mmol) in 60 mL of dimethylformamide is stirred at room temperature overnight. The solution is diluted with 800 mL of ethyl acetate and washed with 1N hydrochloric acid (3x150 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (3:2 hexanes:ethyl acetate).

EXAMPLE 83

Compound 83

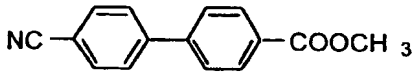


A solution of Compound 81 (2 mmol), acetic anhydride (8 mmol), and dimethylamino pyridine (0.2 mmol) in 20 mL of pyridine is stirred at room temperature overnight. The reaction mixture is poured into 200 mL of 5% hydrochloric acid and extracted with ethyl acetate (3x200 mL). The combined organic extracts are

dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (3:1 hexanes:ethyl acetate).

EXAMPLE 84

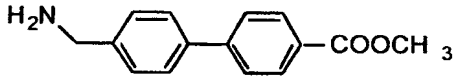
Compound 84



Compound 84 is prepared according to the method described for Compound 74, substituting 4-cyano bromobenzene in the preparation of Solution (A).

EXAMPLE 85

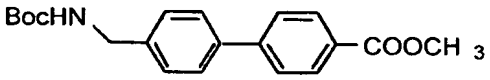
Compound 85



Compound 85 is prepared according to the method described for Compound 81, substituting the product obtained in Example 84.

EXAMPLE 86

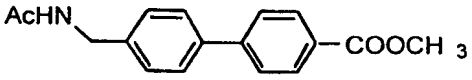
Compound 86



Compound 86 is prepared according to the method described for Compound 82, substituting the product obtained in Example 85.

EXAMPLE 87

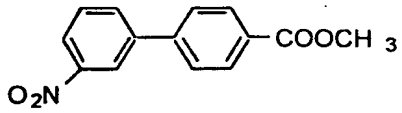
Compound 87



Compound 87 is prepared according to the method described for Compound 83, substituting the product obtained in Example 85.

EXAMPLE 88

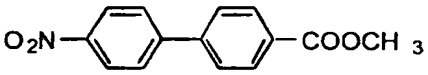
Compound 88



To a solution of methyl coumalate (6.5 mmol) and 3-nitrostyrene (32.5 mmol) in 30 mL of m-xylene is added 10% palladium on carbon (2. 5 g) in a single portion. The reaction mixture is heated at 140°C overnight. After cooling, the reaction mixture is filtered through celite and the filtrate concentrated *in vacuo*. The resulting slurry is triturated with 3:1 hexanes:ethyl acetate. The solid, which is the desired product, is removed by filtration.

EXAMPLE 89

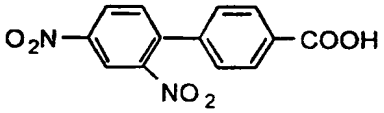
Compound 89



Compound 89 is prepared using a method identical to the one used for Compound 88, substituting 4-nitrostyrene.

EXAMPLE 90

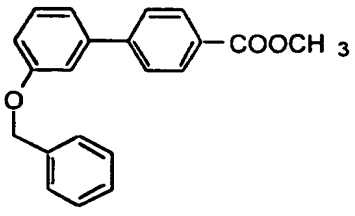
Compound 90



To a flask containing 100 mL of fuming nitric acid is added 4-biphenyl carboxylic acid (20 mmol), portionwise at 0°C. Stirring is continued 15 minutes at 0°C. Water (100 mL) is slowly added and the filtrate collected and recrystallized from ethanol.

EXAMPLE 91

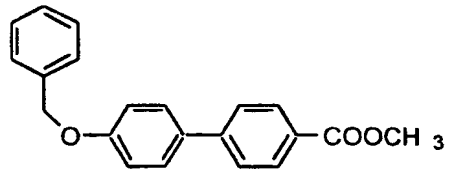
Compound 91



Compound 91 is prepared according to the method described for Compound 74, substituting 3-benzyloxy bromobenzene in the preparation of Solution (A).

EXAMPLE 92

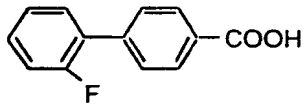
Compound 92



Compound 92 is prepared according to the method described for Compound 74, substituting 4-benzyloxy bromobenzene in the preparation of Solution (A).

EXAMPLE 93

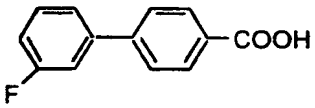
Compound 93



To a suspension of Compound 74 (1.6 mmol) in 10 mL of methanol and 20 mL of tetrahydrofuran is added 10 mL of 2N sodium hydroxide, dropwise at room temperature. The resulting solution is allowed to stir at room temperature for 2 hours. Organic solvents are removed in vacuo and the residue diluted with 20 mL of water and brought to pH 2 with 1N hydrochloric acid. Solid material is filtered off and dried under vacuum.

EXAMPLE 94

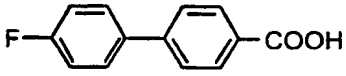
Compound 94



Compound 94 is prepared according to the method described for 93, substituting the product obtained in Example 75.

EXAMPLE 95

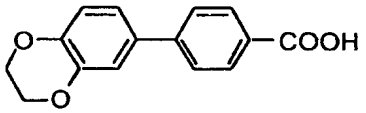
Compound 95



Compound 95 is prepared according to the method described for Compound 93, substituting the product obtained in Example 76.

EXAMPLE 96

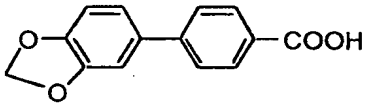
Compound 96



Compound 96 is prepared according to the method described for Compound 93, substituting the product obtained in Example 77.

EXAMPLE 97

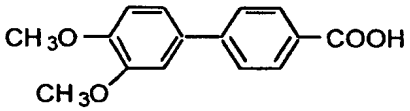
Compound 97



Compound 97 is prepared according to the method described for Compound 93, substituting the product obtained in Example 78.

EXAMPLE 98

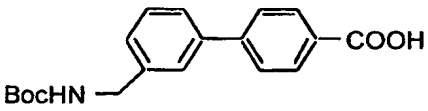
Compound 98



Compound 98 is prepared according to the method described for Compound 93, substituting the product obtained in Example 79.

EXAMPLE 99

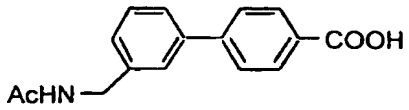
Compound 99



Compound 99 is prepared according to the method described for Compound 93, substituting the product obtained in Example 82.

EXAMPLE 100

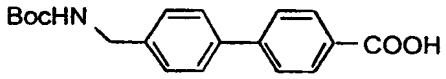
Compound 100



Compound 100 is prepared according to the method described for Compound 93, substituting the product obtained in Example 83.

EXAMPLE 101

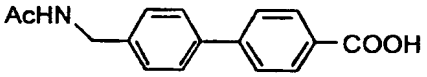
Compound 101



Compound 101 is prepared according to the method described for Compound 93, substituting the product obtained in Example 86.

EXAMPLE 102

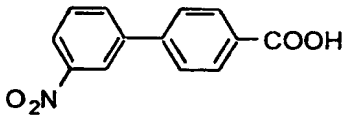
Compound 102



Compound 102 is prepared according to the method described for Compound 93, substituting the product obtained in Example 87.

EXAMPLE 103

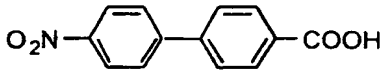
Compound 103



Compound 103 is prepared according to the method described for Compound 93, substituting the product obtained in Example 88.

EXAMPLE 104

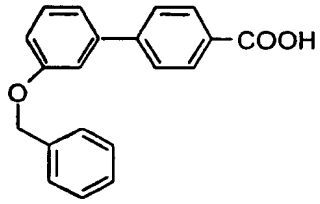
Compound 104



Compound 104 is prepared according to the method described for Compound 93, substituting the product obtained in Example 89.

EXAMPLE 105

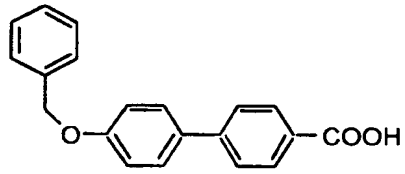
Compound 105



Compound 105 is prepared according to the method described for Compound 93, substituting the product obtained in Example 91.

EXAMPLE 106

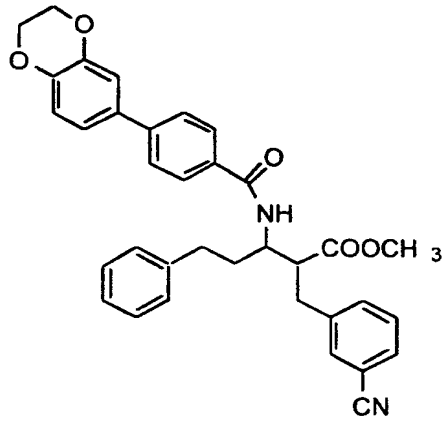
Compound 106



Compound 106 is prepared according to the method described for Compound 93, substituting the product obtained in Example 90.

EXAMPLE 107

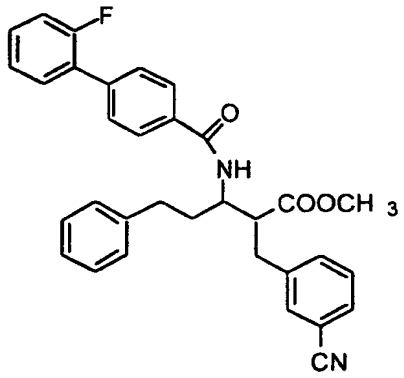
Compound 107



To a solution of Compound 96 (2 mmol) in 10 mL of DMF is added diisopropyl ethylamine (2 mmol) in a single portion at room temperature, followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2 mmol) in a similar fashion. The reaction mixture is stirred for 2 minutes at room temperature and a solution of Compound 70 (2 mmol) in 15 mL of dimethylformamide is added in a single portion. Stirring is continued overnight at room temperature. The reaction mixture is diluted with 300 mL of ethyl acetate and washed sequentially with 1N hydrochloric acid (3x75 mL), water, saturated sodium bicarbonate (3x75 mL) and brine. The organic phase is dried over magnesium sulfate, filtered and concentrated *in vacuo*.

EXAMPLE 108

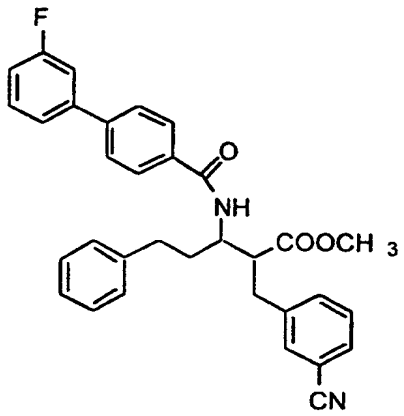
Compound 108



Compound 108 is prepared using the same procedure described for Compound 107, substituting Compound 93 for Compound 96.

EXAMPLE 109

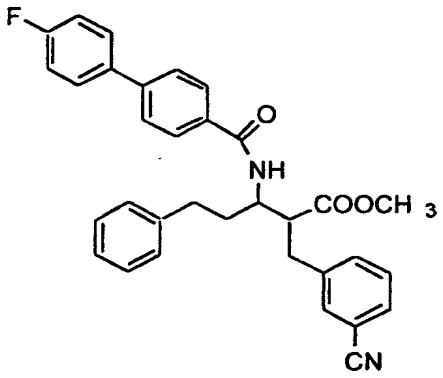
Compound 109



Compound 109 is prepared using the same procedure described for Compound 107, substituting Compound 94 for Compound 96.

EXAMPLE 110

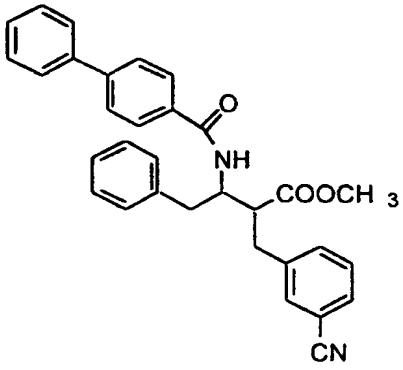
Compound 110



Compound 110 is prepared using the same procedure described for Compound 107, substituting Compound 95 for Compound 96.

EXAMPLE 111

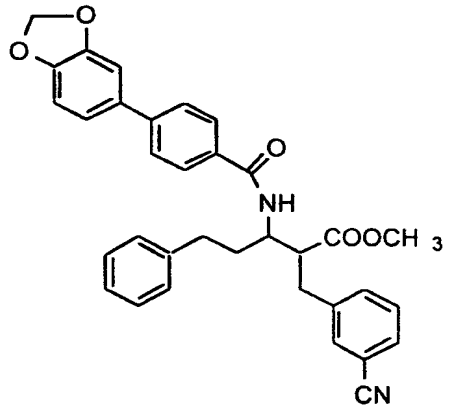
Compound 111



Compound 111 is prepared using the same procedure described for Compound 107, substituting 4-biphenyl carboxylic acid for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 112

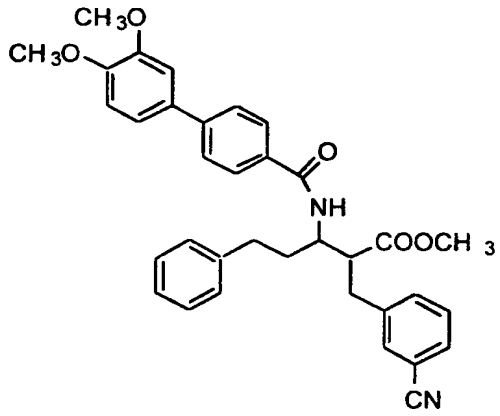
Compound 112



Compound 112 is prepared using the same procedure described for Compound 107, substituting Compound 97 for Compound 96.

EXAMPLE 113

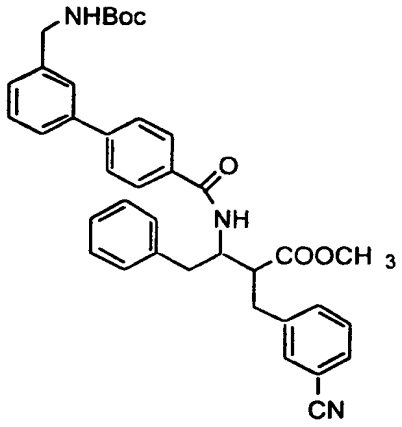
Compound 113



Compound 113 is prepared using the same procedure described for Compound 107, substituting Compound 98 for Compound 96.

EXAMPLE 114

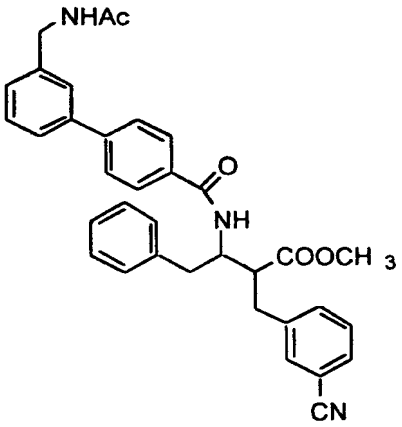
Compound 114



Compound 114 is prepared using the same procedure described for Compound 107, substituting Compound 99 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 115

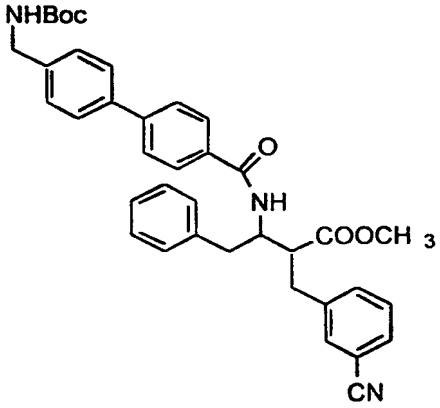
Compound 115



Compound 115 is prepared using the same procedure described for Compound 107, substituting Compound 100 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 116

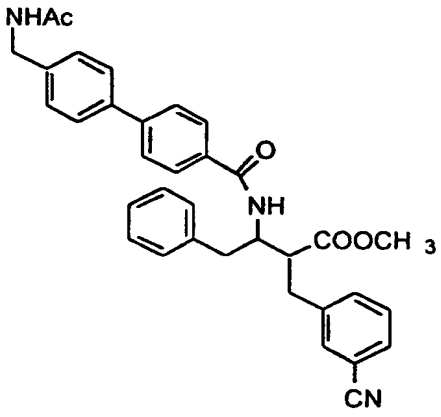
Compound 116



Compound 116 is prepared using the same procedure described for Compound 107, substituting Compound 101 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 117

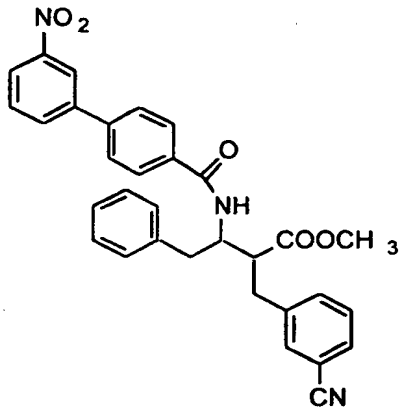
Compound 117



Compound 117 is prepared using the same procedure described for Compound 107, substituting Compound 102 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 118

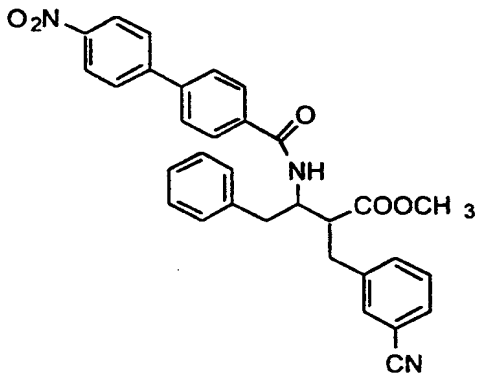
Compound 118



Compound 118 is prepared using the same procedure described for Compound 107, substituting Compound 103 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 119

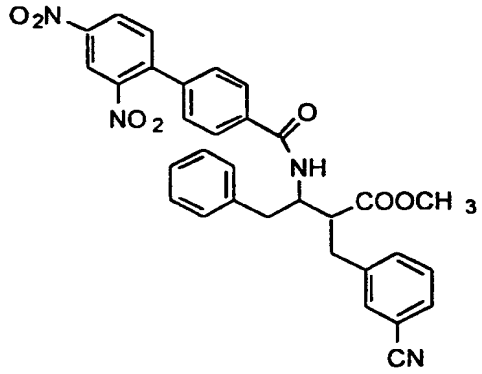
Compound 119



Compound 119 is prepared using the same procedure described for Compound 107, substituting Compound 104 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 120

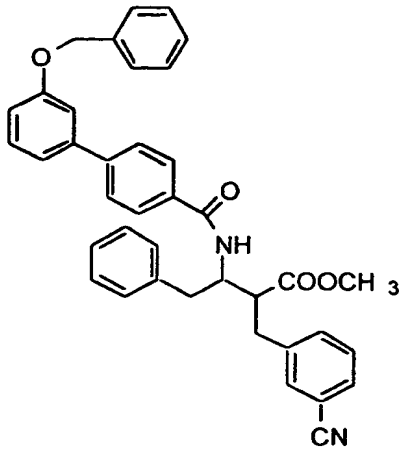
Compound 120



Compound 120 is prepared using the same procedure described for Compound 107, substituting Compound 90 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 121

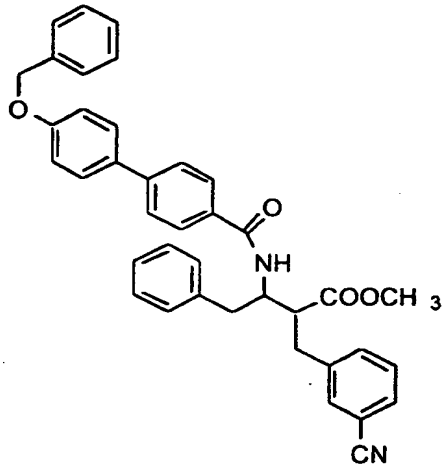
Compound 121



Compound 121 is prepared using the same procedure described for Compound 107, substituting Compound 105 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 122

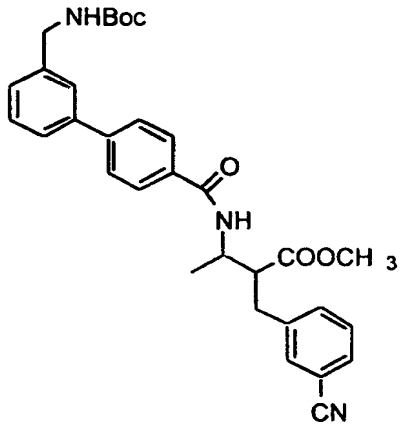
Compound 122



Compound 122 is prepared using the same procedure described for Compound 107, substituting Compound 106 for Compound 96 and substituting Compound 68 for Compound 70.

EXAMPLE 123

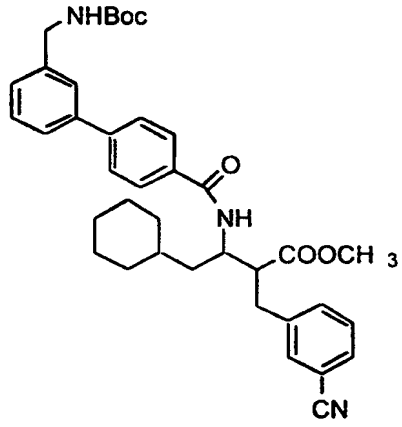
Compound 123



Compound 123 is prepared using the same procedure described for Compound 107, substituting Compound 99 for 96 and substituting Compound 69 for Compound 70.

EXAMPLE 124

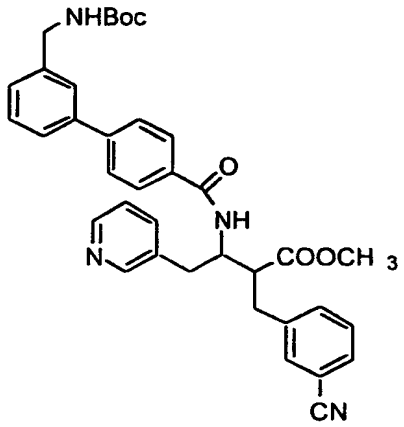
Compound 124



Compound 124 is prepared using the same procedure described for Compound 107, substituting Compound 99 for Compound 96 and substituting Compound 73 for Compound 70.

EXAMPLE 125

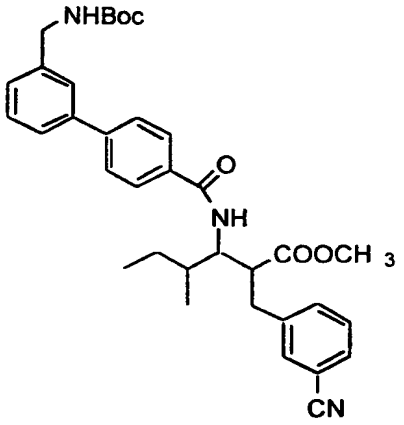
Compound 125



Compound 125 is prepared using the same procedure described for Compound 107, substituting Compound 99 for Compound 96 and substituting Compound 71 for Compound 70.

EXAMPLE 126

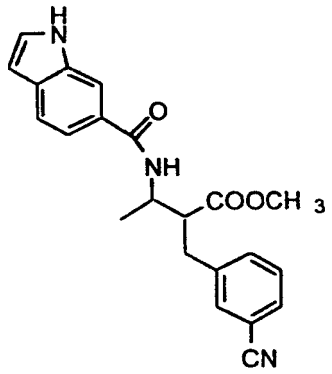
Compound 126



Compound 126 is prepared using the same procedure described for Compound 107, substituting Compound 99 for Compound 96 and substituting Compound 72 for Compound 70.

EXAMPLE 127

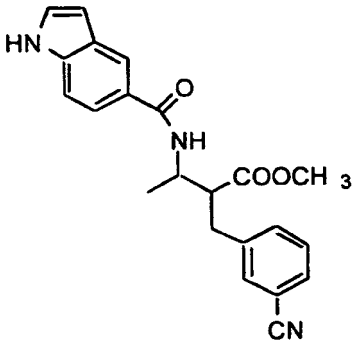
Compound 127



Compound 127 is prepared using the same procedure described for Compound 107, substituting indole-6-carboxylic acid for Compound 96 and substituting Compound 69 for Compound 70.

EXAMPLE 128

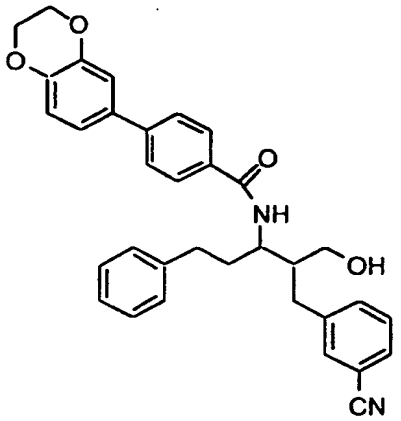
Compound 128



Compound 128 is prepared using the same procedure described for Compound 107, substituting indole-5-carboxylic acid for Compound 96 and substituting Compound 69 for Compound 70.

EXAMPLE 129

Compound 129

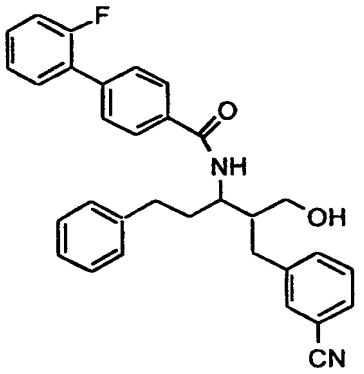


To a solution of Compound 107 (1.2 mmol) in 10 mL of methanol and 10 mL of tetrahydrofuran is added 10 mL of 2N sodium hydroxide, dropwise at 0°C. The solution is allowed to come to room temperature and stirred at room temperature for 2.5 hours. The solution is cooled to 0°C and 1N hydrochloric acid is added until the pH is 7. Organic solvents are removed *in vacuo* and the residue diluted with 25 mL of water. 1N hydrochloric acid is added to bring the pH down to 2 and the mixture is extracted with ethyl acetate (3x75 mL). The combined organic extracts are dried over magnesium sulfate, filtered, concentrated, and dried under vacuum.

The acid (1.1 mmol) is dissolved in 15 mL of tetrahydrofuran and cooled to -20°C. N-methyl morpholine (1.45 mmol) is added in a single portion, followed by isobutyl chloroformate (1.45 mmol) dropwise via syringe. The reaction mixture is allowed to stir at -20°C for 20 minutes. The reaction mixture is filtered into a solution of sodium borohydride (11 mmol) in 20 mL of water at 0°C. Stirring is continued 1.5 hours at 0°C. The reaction mixture is diluted with 300 mL of ethyl acetate and washed with water (3x100 mL) and brine. The organic phase is dried over magnesium sulfate, filtered, and concentrated. The resulting alcohol is purified by flash chromatography (2:3 ethyl acetate:hexanes).

EXAMPLE 130

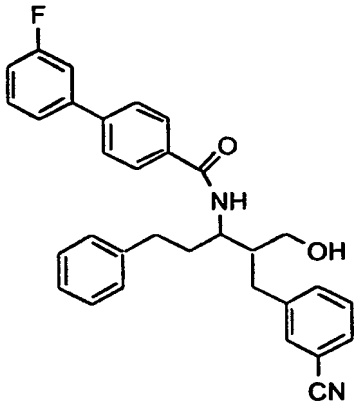
Compound 130



Compound 130 is prepared following the procedure described for Compound 129, substituting Compound 108 for Compound 107.

EXAMPLE 131

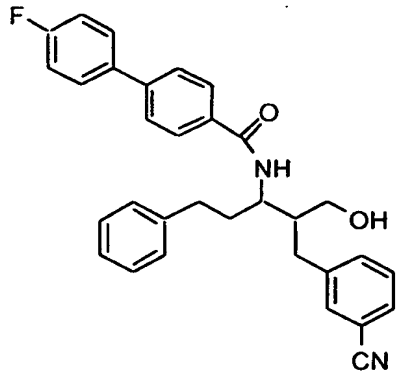
Compound 131



Compound 131 is prepared following the procedure described for Compound 129, substituting Compound 109 for Compound 107.

EXAMPLE 132

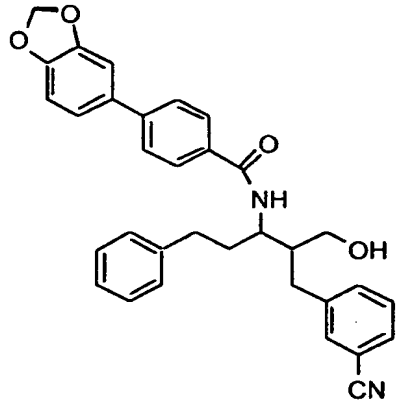
Compound 132



Compound 132 is prepared following the procedure described for Compound 129, substituting Compound 110 for Compound 107.

EXAMPLE 133

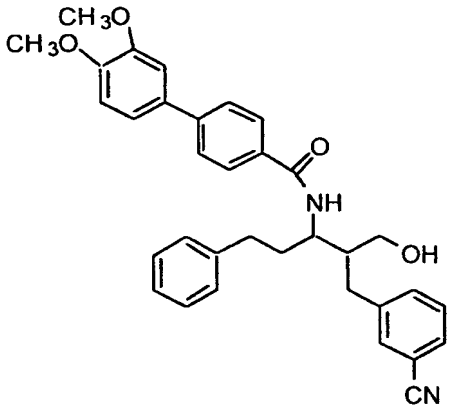
Compound 133



Compound 133 is prepared following the procedure described for Compound 129, substituting Compound 112 for Compound 107.

EXAMPLE 134

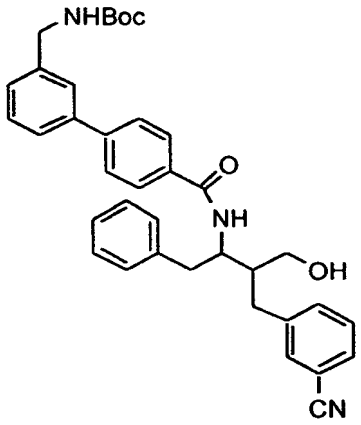
Compound 134



Compound 134 is prepared following the procedure described for Compound 129, substituting Compound 113 for Compound 107.

EXAMPLE 135

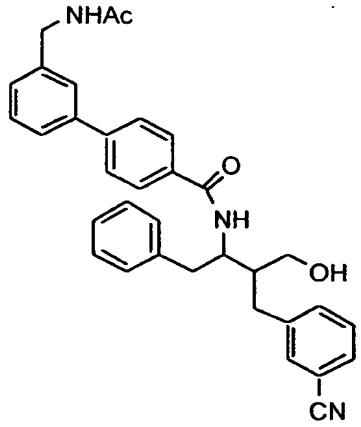
Compound 135



Compound 135 is prepared following the procedure described for Compound 129, substituting Compound 114 for Compound 107.

EXAMPLE 136

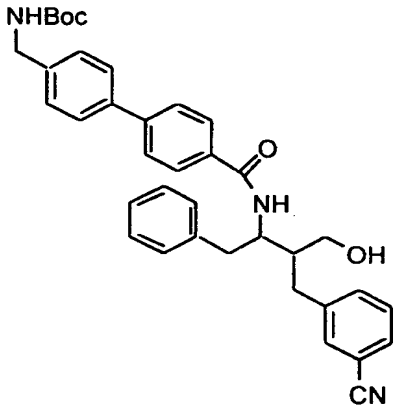
Compound 136



Compound 136 is prepared following the procedure described for Compound 129, substituting Compound 115 for Compound 107.

EXAMPLE 137

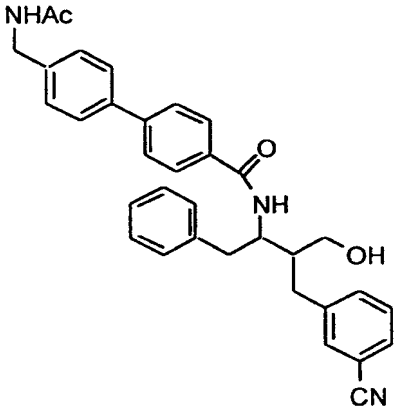
Compound 137



Compound 137 is prepared following the procedure described for Compound 129, substituting Compound 116 for Compound 107.

EXAMPLE 138

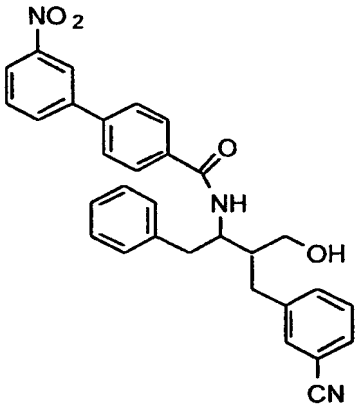
Compound 138



Compound 138 is prepared following the procedure described for Compound 129, substituting Compound 117 for Compound 107.

EXAMPLE 139

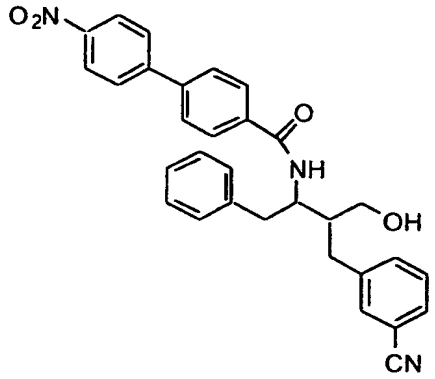
Compound 139



Compound 139 is prepared following the procedure described for Compound 129, substituting Compound 118 for Compound 107.

EXAMPLE 140

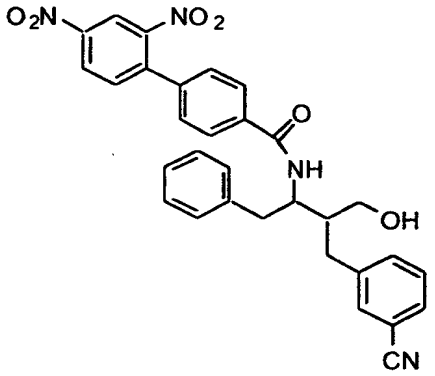
Compound 140



Compound 140 is prepared following the procedure described for Compound 129, substituting Compound 119 for Compound 107.

EXAMPLE 141

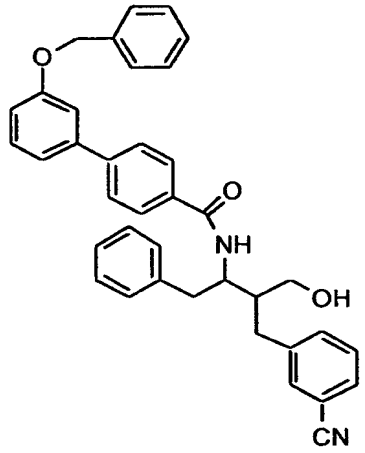
Compound 141



Compound 141 is prepared following the procedure described for Compound 129, substituting Compound 120 for Compound 107.

EXAMPLE 142

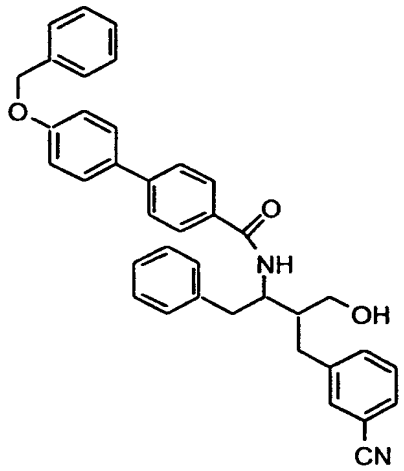
Compound 142



Compound 142 is prepared following the procedure described for Compound 129, substituting Compound 121 for Compound 107.

EXAMPLE 143

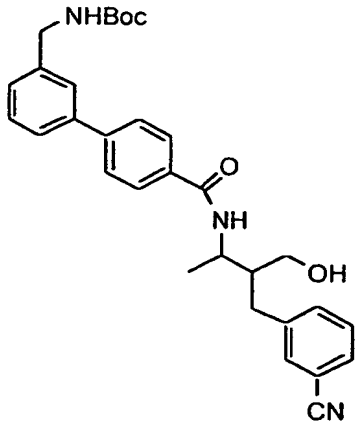
Compound 143



Compound 143 is prepared following the procedure described for Compound 129, substituting Compound 122 for Compound 107.

EXAMPLE 144

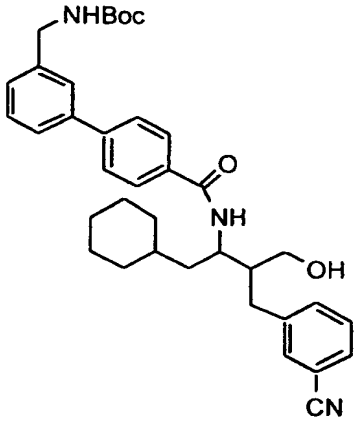
Compound 144



Compound 144 is prepared following the procedure described for Compound 129, substituting Compound 123 for Compound 107.

EXAMPLE 145

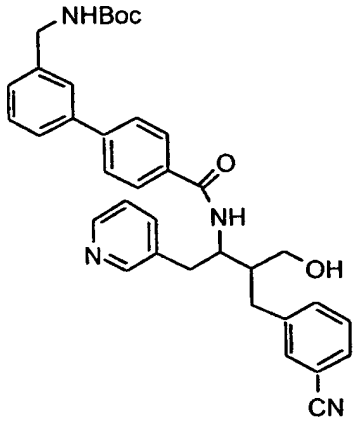
Compound 145



Compound 145 is prepared following the procedure described for Compound 129, substituting Compound 124 for Compound 107.

EXAMPLE 146

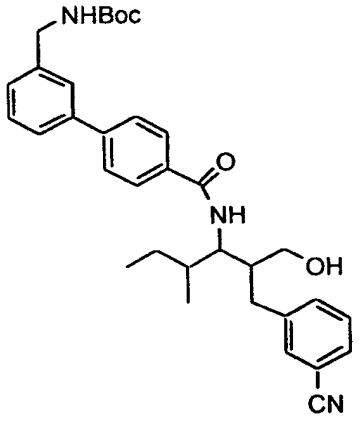
Compound 146



Compound 146 is prepared following the procedure described for Compound 129, substituting Compound 125 for Compound 107.

EXAMPLE 147

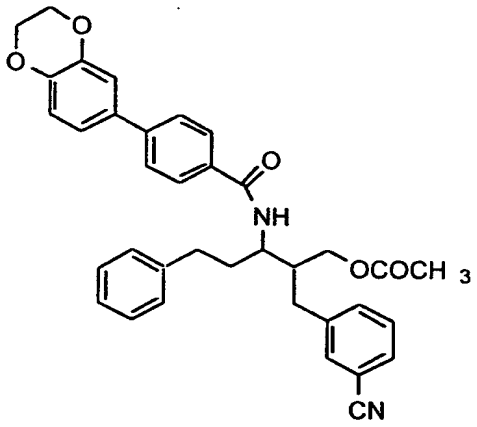
Compound 147



Compound 147 is prepared following the procedure described for Compound 129, substituting Compound 126 for Compound 107.

EXAMPLE 148

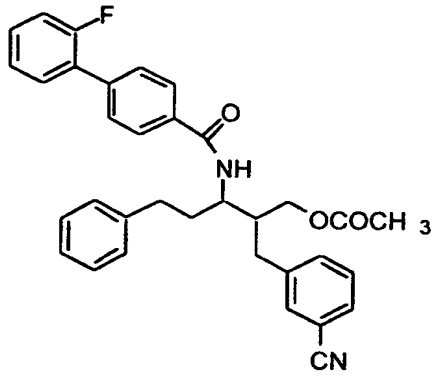
Compound 148



To a solution of Compound 129 (0.5 mmol) in 8 mL of methylene chloride is added pyridine (0.6 mmol) in a single portion at 0°C. Acetic anhydride (0.6 mmol) is added in a single portion, followed by dimethylaminopyridine in a similar fashion. The reaction mixture is allowed to come to room temperature and stirring is continued overnight. The reaction mixture is partitioned between 10 mL of 0.1N hydrochloric acid and 30 mL of methylene chloride. The organic layer is dried over sodium sulfate, filtered and concentrated *in vacuo*.

EXAMPLE 149

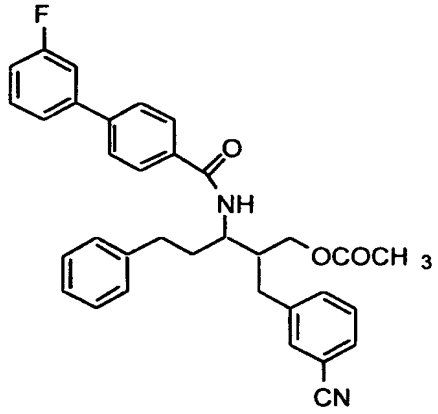
Compound 149



Compound 149 is prepared following the method described for Compound 148, substituting Compound 130 for Compound 129.

EXAMPLE 150

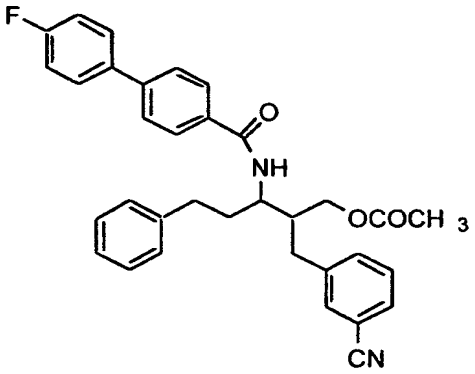
Compound 150



Compound 150 is prepared following the method described for Compound 148, substituting Compound 131 for Compound 129.

EXAMPLE 151

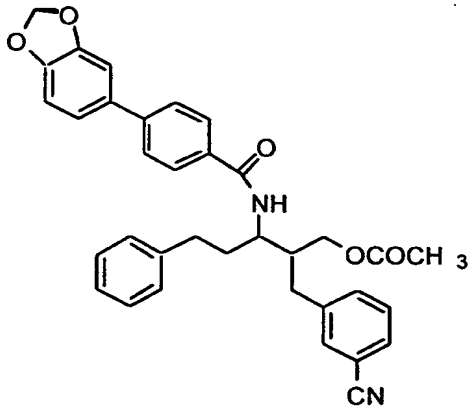
Compound 151



Compound 151 is prepared following the method described for Compound 148, substituting Compound 132 for Compound 129.

EXAMPLE 152

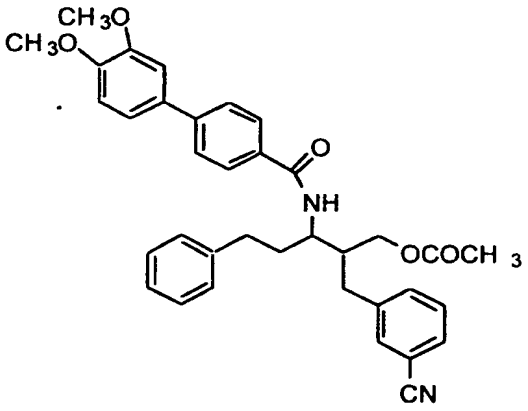
Compound 152



Compound 152 is prepared following the method described for Compound 148, substituting Compound 133 for Compound 129.

EXAMPLE 153

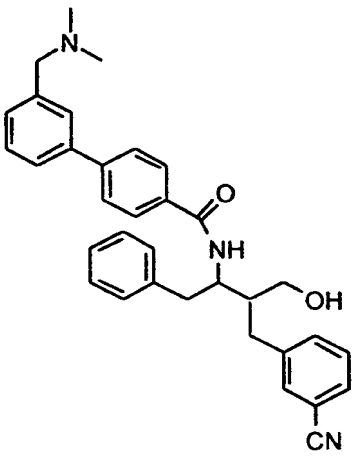
Compound 153



Compound 153 is prepared following the method described for Compound 148, substituting Compound 134 for Compound 129.

EXAMPLE 154

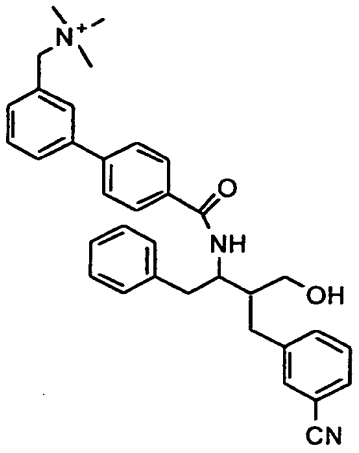
Compound 154



To a solution of Compound 135 (1.1 mmol) in 30 mL of methylene chloride is added 10 mL of trifluoroacetic acid in a single portion at 0°C. The resulting solution is stirred for 3 hours at 0°C. Solvents are removed *in vacuo* and the residue partitioned between 10% aqueous sodium bicarbonate and ethyl acetate. The organic phase is dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The free amine (1.1 mmol) is dissolved in 10 mL of glacial acetic acid and paraformaldehyde (11 mmol) is added in a single portion at room temperature. Stirring is continued overnight at room temperature. The reaction mixture is poured into 50 mL of ice cold 2N sodium hydroxide and extracted with ethyl acetate (3x100 mL). The combined organic extracts are backwashed with water, dried over magnesium sulfate, filtered, and concentrated in vacuo. The desired product is purified by reverse phase HPLC using a gradient of 20% to 100% acetonitrile in water, buffered with 0.1% trifluoroacetic acid.

EXAMPLE 155

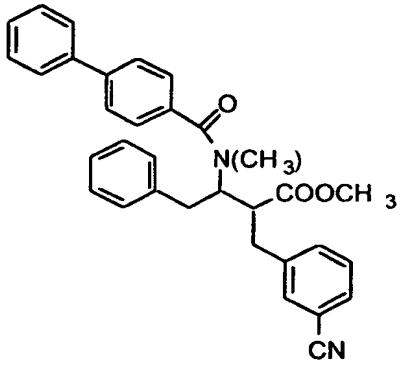
Compound 155



To a solution of Compound 154 (0.5 mmol) in 10 mL of dry acetone is added methyl iodide (large excess, 2 mL) in a single portion at room temperature. The resulting solution is allowed to stir at room temperature overnight. Solvents are removed in vacuo to provide the desired tetramethylammonium salt.

EXAMPLE 156

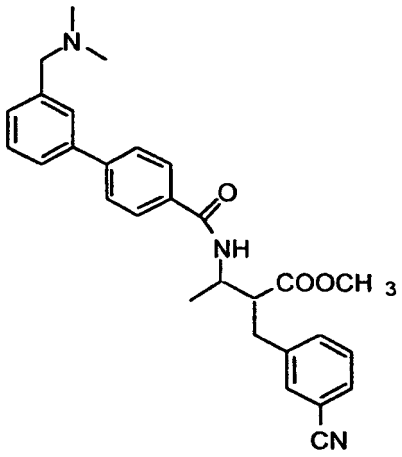
Compound 156



To a solution of Compound 111 (0.8 mmol) in 2 mL of dimethylformamide and 8 mL of tetrahydrofuran is added sodium hydride (1 mmol) in a single portion at 0°C. The solution is stirred for 1 hour at 0°C and methyl iodide (large excess) is added in a single portion. The solution is allowed to come to room temperature and stirred overnight. The reaction mixture is poured into 100 mL of ice water and extracted with ethyl acetate (3x75 mL). The combined organic extracts are backwashed with water, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (1:2 ethyl acetate:hexanes).

EXAMPLE 157

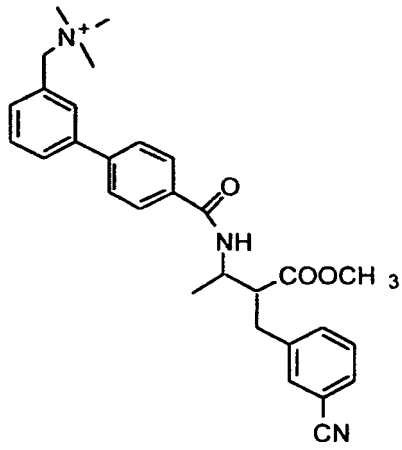
Compound 157



Compound 157 is prepared following the procedure described for Compound 154, substituting Compound 123 for 135.

EXAMPLE 158

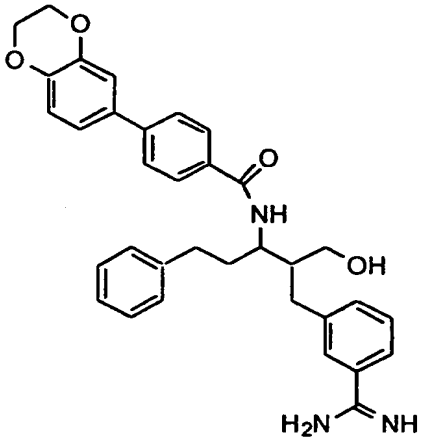
Compound 158



Compound 158 is prepared according to the method described for Compound 155, starting from Compound 157.

EXAMPLE 159a

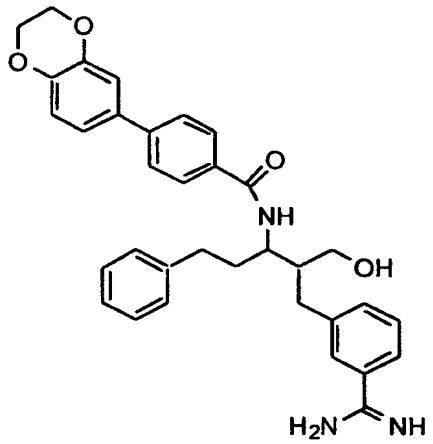
Compound 159



To a solution of Compound 129 (1 mmol) in 50 mL of dry methanol is added crushed 3Å molecular sieves (approximately 1g). The mixture is stirred for 10 minutes at 0°C and hydrogen chloride gas is bubbled through the reaction mixture for 10 minutes at 0°C. The reaction mixture is allowed to come to room temperature and stirred overnight. Nitrogen gas is bubbled through the reaction mixture for 5 minutes and methanol is removed *in vacuo*. The residue is dried under vacuum to remove all traces of hydrogen chloride, then remixed with 75 mL of dry methanol. The mixture is then cooled to 0°C and ammonia gas is bubbled through the reaction mixture for 10 minutes. The reaction mixture is allowed to come to room temperature, then heated at 60°C for 3 hours. After cooling to room temperature, nitrogen gas is bubbled through the reaction for 5 minutes and the mixture is filtered through celite, concentrated *in vacuo*, and purified by reverse phase HPLC using a gradient of 20% to 80% acetonitrile in water buffered with 0.1% trifluoroacetic acid. Acetonitrile is removed *in vacuo* and the aqueous phase lyophilized to provide the desired product as its trifluoroacetate salt.

EXAMPLE 159b

Compound 159



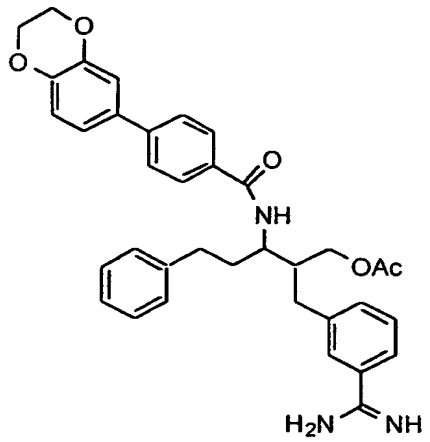
^{1}H NMR (300 MHz, d6 DMSO) δ 9.21 (s, 2H), 9.01 (s, 2H), 8.22 (d, 1H, J=9.6 Hz), 7.85 (d, 2H,J=7.2 Hz), 7.70 (d, 2H, J=7.2 Hz), 7.62-7.38 (m, 4H), 7.25-7.05 (m, 7H), 6.93 (d, 1H, J=8.4 Hz), 4.90-4.65 (m, 1H), 4.24 (s, 4H), 4.18-4.05 (m, 2H), 2.78-2.63 (m, 2H), 2.65-2.45 (m, 2H), 2.08-1.75 (m,3H). MS, LRFAB, calc.591, found 592 (M+H)+.

Into a solution of Compound 129 (1 mmol) in 20 mL of pyridine and 4 mL of triethylamine is bubbled hydrogen sulfide for 10 minutes at room temperature. The solution is allowed to stir at room temperature overnight. Nitrogen gas is bubbled through the reaction for 5 minutes and solvents are removed *in vacuo*. The residue is dried under vacuum, then dissolved in 15 mL of dry acetone. To this solution is added 5 mL of methyl iodide and this solution is heated at 50°C for 1 hour, then concentrated *in vacuo*. The residue is dissolved in 20 mL of methanol and ammonium acetate (2 mmol) is added in a single portion at room temperature. The reaction mixture is heated at 65°C for 2 hours. After cooling, methanol is removed in vacuo and the residue purified by reverse phase HPLC using a gradient of 20% to 80% acetonitrile in water buffered with 0.1% trifluoroacetic acid. Acetonitrile is removed *in vacuo* and the aqueous phase lyophilized to provide the desired product as its trifluoroacetate salt.

The following compounds are prepared from the appropriate starting materials by procedures substantially similar to the procedures described above.

EXAMPLE 161

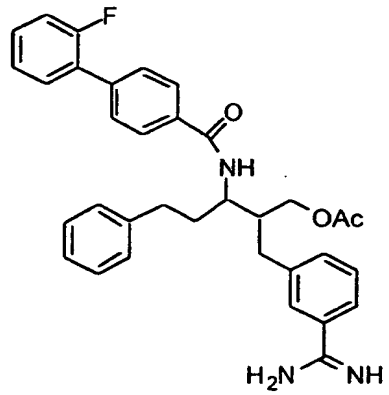
Compound 161



^{1}H NMR (300 MHz, d6 DMSO) δ 9.23 (s, 2H), 9.01 (s, 2H), 8.27 (d, 1H, J=9.6 Hz), 7.93 (d, 2H, J=7.2 Hz), 7.72 (d, 2H, J=7.2 Hz), 7.65-7.55 (m, 2H), 7.54-7.42 (m, 2H), 7.28-7.08 (m, 7H), 6.94 (d, 1H, J=8.4 Hz), 4.25 (s, 4H), 4.24-4.11 (m,1H), 4.05-3.83 (m,2H), 2.86 (dd, 1H, J=6.0, 15.6 Hz), 2.70-2.55 (m, 2H), 2.53-2.43 (m,1H), 2.35-2.20 (m,1H), 1.98-1.90 (m ,2H), 1.87 (s, 3H). MS, LRFAB, calc.591, found 592 (M+H)+.

EXAMPLE 162

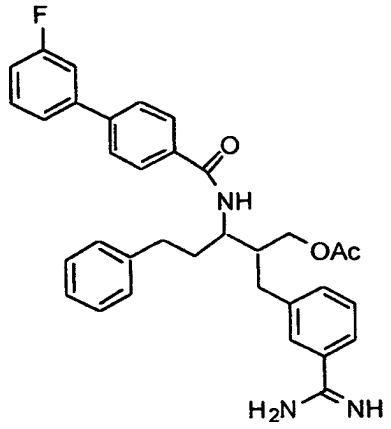
Compound 162



^{1}H NMR (300 MHz, d6 DMSO) δ 9.21 (s, 2H), 9.01 (s, 2H), 8.22 (d, 1H, J=9.6 Hz), 7.85 (d, 2H,J=7.2 Hz), 7.70 (d, 2H, J=7.2 Hz), 7.62-7.38 (m, 4H), 7.25-7.05 (m, 7H), 6.93 (d, 1H, J=8.4 Hz), 4.90-4.65 (m, 1H), 4.24 (s, 4H), 4.18-4.05 (m, 2H), 2.78-2.63 (m, 2H), 2.65-2.45 (m, 2H), 2.08-1.75 (m,3H). MS, LRFAB, calc.591, found 592 (M+H)+.

EXAMPLE 163

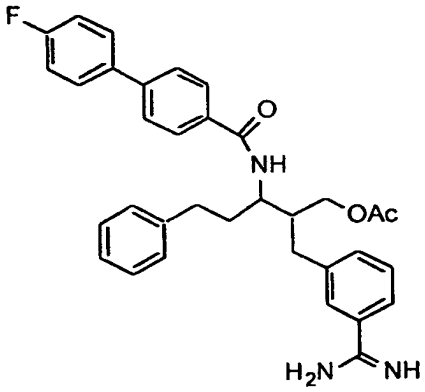
Compound 163



^{1}H NMR 300 MHz, d6 DMSO, δ 9.23 (s, 2H), 9.09 (s, 2H), 8.83 (d, 1H, J=9.6 Hz), 7.97 (d, 2H, J=7.2 Hz), 7.83 (d, 1H, J=7.2 Hz), 7.65-7.35 (m, 7H), 7.28-7.05 (m, 6H), 4.26-4.10 (m,1H), 4.05-3.83 (m, 2H), 2.87 (dd, 1H, J=6.0 Hz,15.6 Hz), 2.70-2.55 (m, 2H), 2.32-2.18 (m, 1H), 2.03-1.90 (m, 2H), 1.87(s, 3H). MS ion spray: calc. 551, found 552 (M+H)+.

EXAMPLE 164

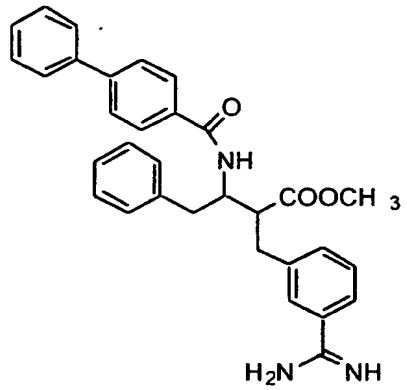
Compound 164



^{1}H NMR 300 MHz, d6 DMSO, δ 9.22 (s, 2H), 9.02 (s, 2H), 8.32 (d, 1H, J=9.6 Hz), 7.96 (d, 2H, J=7.2 Hz), 7.81-7.65 (m, 4H), 7.65-7.40 (m, 4H), 7.38-7.05 (m, 7H), 4.25-4.10 (m, 1H), 4.05-3.85 (m, 2H), 2.87 (dd, 1H, J=6.0,15.6Hz), 2.70-2.55 (m, 2H), 2.54-2.43 (m, 1H), 2.35-2.20 (m, 1H), 1.98-1.90 (m, 2H),1.89 (s, 3H). MS ion spray: calc. 551, found 552 (M+H)+.

EXAMPLE 165

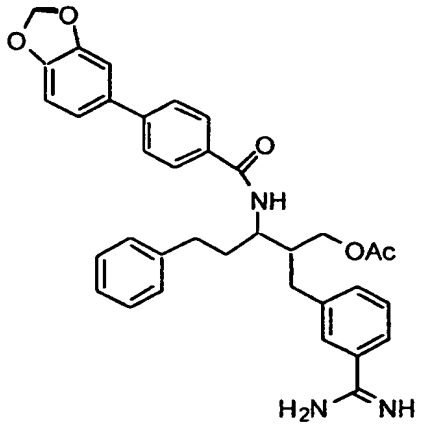
Compound 165



^{1}H NMR, 300 MHz, d6 DMSO, δ 9.25 (s, 2H), 9.18 (s, 2H), 8.35 (d, 1H, J=9.6 Hz), 7.80 (d, 2H, 7.2 Hz), 7.73 (d, 2H, J=7.2 Hz), 7.68 (d, 2H, J=6.0 Hz), 7.62 (br.s, 2H), 7.55-7.31 (m, 5H), 7.25-7.03 (m, 5H), 4.65-4.45 (m, 1H),3.53 (s, 3H), 3.20-2.82 (m, 5H). MS LRFAB: cal'd 505, found 506 (M+H)+.

EXAMPLE 166

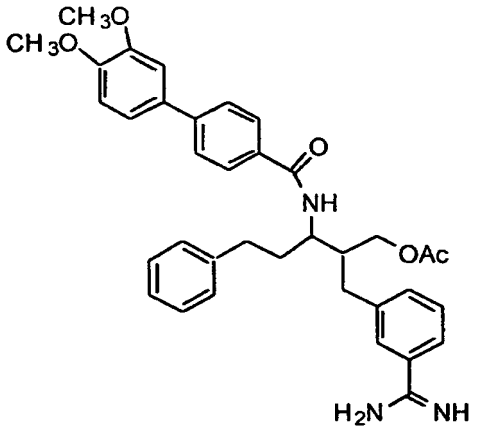
Compound 166



^{1}H NMR (300 MHz, d6 DMSO) δ 9.23 (s, 2H), 8.99 (s, 2H), 8.26 (d, 1H, J=9.6 Hz), 7.93 (d, 2H, J=7.2 Hz), 7.72 (d, 2H, J=7.2 Hz), 7.65-7.56 (m, 2H), 7.54-7.42 (m, 2H), 7.32 (d, 1H, J=2.4 Hz), 7.28-7.08 (m, 6H), 7.02 (d, 1H, J=8.4 Hz), 6.07 (s, 2H), 4.25-4.12 (m, 1H), 4.06-3.85 (m, 2H), 2.85 (dd, 1H, J=6.0, 15.6 Hz), 2.68-2.55 (m, 2H), 2.53-2.43 (m, 1H), 2.32-2.20 (m, 1H), 2.01-1.90 (m, 2H), 1.87 (s, 3H). MS, LRFAB, calc.557, found 558 (M+H)+.

EXAMPLE 167

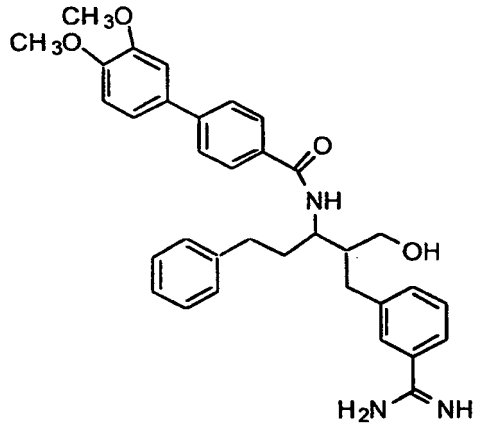
Compound 167



^{1}H NMR: 9.5 (s, 1H), 9.4 (s, 1H), 8.4 (d, ^{1}H J=9.0 Hz), 8.1 (d, 2H, J=8.0 Hz), 7.9 (d, 2H, J=8.0 Hz), 7.5-7.8 (m, 5H), 7.1-7.4 (m, 7H), 5.0 (m, 1H), 4.0-4.1 (m, 1H), 4.0 (s, 3H), 3.9 (s, 3H), 3.6 (m, 1H), 2.9-3.1 (m, 4H), 2.1-2.3 (m, 2H), 2.0 (s, 3H). M.S. Cal'd 594.3, Found 594.

EXAMPLE 168

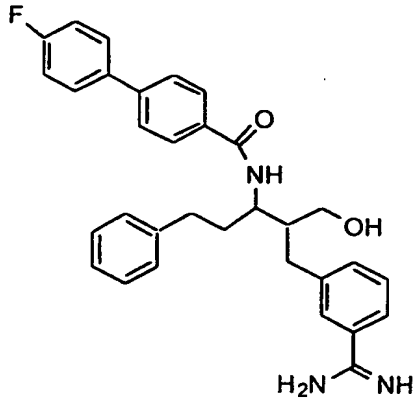
Compound 168



^{1}H NMR: 9.4 (s, 1H), 9.0 (s, 1H), 8.4 (d, 1H, J=9.0 Hz), 8.1 (d, 2H, J=7.0 Hz), 7.9 (d, 2H, J=7.0 Hz), 7.5-7.8 (m, 5H), 7.1-7.4 (m, 7H), 5.0 (m, 1H), 4.0-4.1 (m, 1H), 4.0 (s, 3H), 3.9 (s, 3H), 3.6 (m, H), 2.9-3.1 (m, 4H), 2.1-2.3 (m, 2H). M.S. Cal'd 552.1, Found 552

EXAMPLE 169

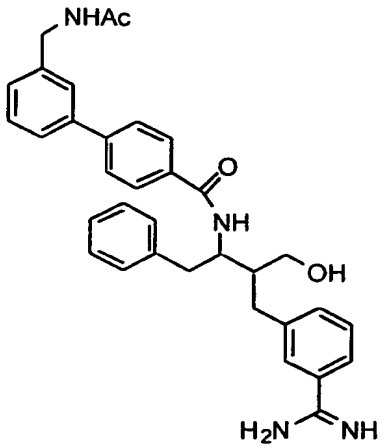
Compound 169



^{1}H NMR, 300 MHz, d6 DMSO, δ 9.22 (s, 2H), 9.11 (s, 2H), 7.92 (d, 2H, J=7.2 Hz), 7.80- 7.65 (m, 4H), 7.62-7.40 (m, 4H), 7.37-7.01 (m, 7H), 4.85-4.65 (m, 1H), 4.22-4.02 (m, 1H), 3.55-3.36 (m, 2H), 2.82-2.62 (m, 2H), 2.60-2.45 (m, 1H), 2.05-1.73 (m, 3H). MS LRFAB: calc. 509, found 510 (M+H).

EXAMPLE 170

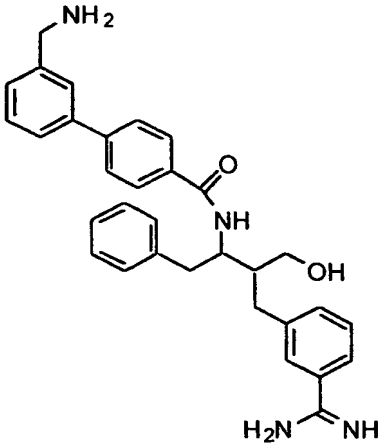
Compound 170



^{1}H NMR: 8.5 (d, 1H, J=9.0 Hz), 7.8 (d, 2H, J=9.0 Hz), 7.7 (d, 2H, J=9.0 Hz), 7.1-7.6 (m, 11H), 4.5 (m, 1H), 4.4 (s, 2H), 4.0 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.7 (dd, 1H,(J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 2H, J=9.0 Hz), 2.0 (d, 1H, J=7.0 Hz). Mass spec M+H calc 549.2, found 549.

EXAMPLE 171

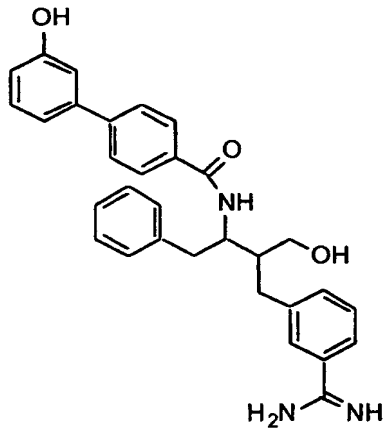
Compound 171



^{1}H NMR: 8.5 (d, 1H, J=9.0 Hz), 7.75-7.9 (m, 6H), 7.4-7.7 (m, 6H), 7.0-7.2 (m, 5H), 4.4(m, 1H), 4.2 (s, 2H), 4.0 (dd, 1H, (J=6.0 Hz,10.0 Hz), 3.7 (dd,1H, J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 1H, (J=9.0 Hz), 2.0 (m, 1H). Mass spec M+H calc 507.3, found 507.

EXAMPLE 172

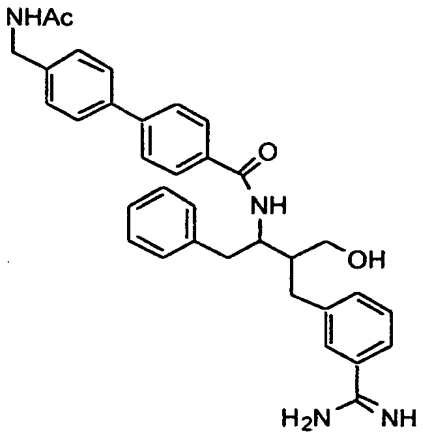
Compound 172



^{1}H NMR: 8.5 (d, 1H, J=9.0 Hz), 7.8 (d, 2H, J=10.0 Hz), 7.7 (d, 2H, J=10.0 Hz), 7.6 (d, 1H, J=10.0 Hz), 7.5 (m, 3H), 7.0-7.3 (m, 8H), 6.8 (d, 1H, J=9.0 Hz), 4.5 (m, 3H), 4.1 (dd, 1H, J=6.0 Hz, 10.0 Hz), 3.9 (dd, H J=6.0 Hz, 10.0 Hz), 3.1 (d, 2H,J=9.0 Hz) 2.9 (d, 2H,J=9.0 Hz), 2.0 (m, 1H). Mass Spec M+H calc 494.2, found 494.

EXAMPLE 173

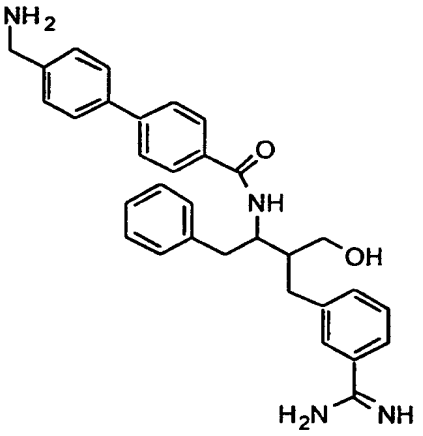
Compound 173



^{1}H NMR: 8.5 (d, 1H, J=9.0 Hz), 7.9 (d, 2H, J=10.0 Hz), 7.8 (d, 2H, J=10.0 Hz), 7.7 (d, 2H, J=10.0 Hz), 7.6 (d, 2H, J=10.0 Hz), 7.4 (s, 1H), 7.0-7.2 (m, 3H), 4.5 (m, 3H), 4.1 (dd, H, J=6.0 Hz,10.0 Hz), 3.9 (dd, ^{1}H J=6.0 Hz,10.0 Hz), 3.1 (d, 2H, J=9.0 Hz) 2.9 (d, 2H,J=9.0 Hz), 2.1 (d, 3H, J=10.0 Hz). Mass Spec M+H calc 549.3, found 549.

EXAMPLE 174

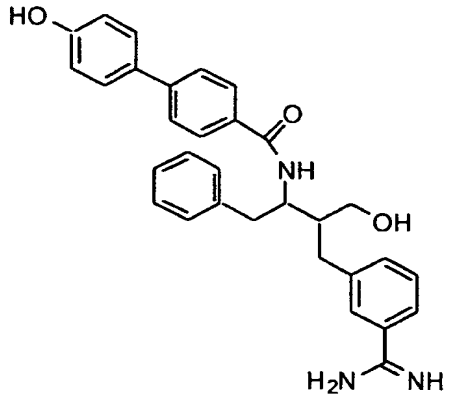
Compound 174



^{1}H NMR: 8.5 (d, 1H, J=9.0 Hz), 7.8 (d, 2H, J=8.0 Hz), 7.6-7.8 (m,4H), 7.4-7.6 (m, 4H), 7.1-7.3 (m, 4H), 6.8 (d, 2H, J=9.0 Hz), 4.3 (m, 1H), 4.0 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.7 (dd, 1H, J=6.0 Hz, 10.0 Hz), 3.0 (d, 2H, J=4.0 Hz), 2.9 (d, 1H, J=9.0 Hz), 2.0 (m, 1H). Mass spec. M+H calc 507.3, found 507

EXAMPLE 175

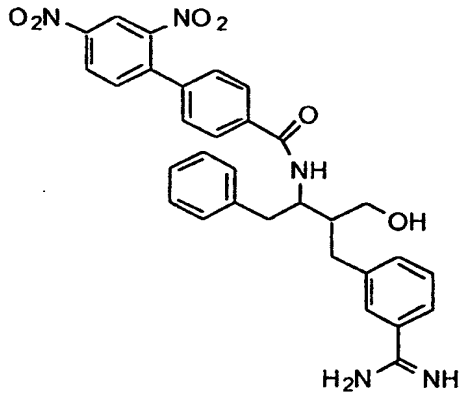
Compound 175



M.S. Cal'd 494.2, Found 494

EXAMPLE 176

Compound 176

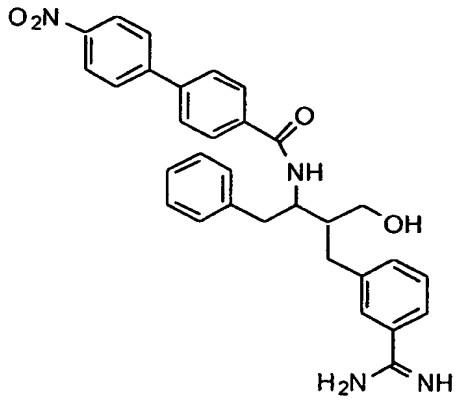


^{1}H NMR 300 MHz, d6 DMSO δ 9.23 (s, 2H), 9.04 (s, 2H), 8.57 (d, 1H, 9.6 Hz), 8.42 (s, 1H), 8.32 (d, 2H, 7.2 Hz), 8.13 (dd, 1H, J=1.2, 7.2 Hz), 7.75-7.40 (m, 7H), 7.25-7.13 (m, 4H), 7.12-7.05 (m, 2H), 4.48-4.35 (m, 1H), 3.58-3.42 (m, 2H), 3.10-2.62 (m, 4H), 2.15-1.95 (m, 1H).

MS (LRFAB): calc. 567, found 568 (M+H)+.

EXAMPLE 177

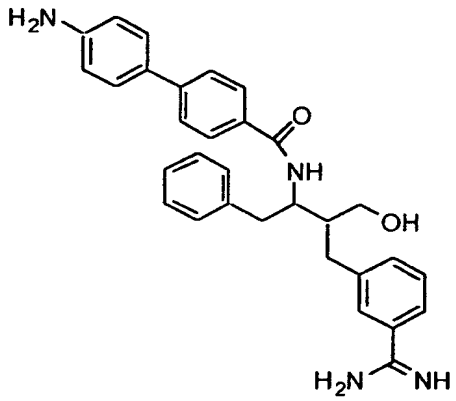
Compound 177



^{1}H NMR 300 MHz, d6 DMSO δ 9.23 (s, 2H), 8.98 (s, 2H), 8.37-8.22 (m,3H), 7.97 (d, 2H, J=7.2 Hz), 7.86 (s, 4H), 7.65-7.40 (m, 4H), 7.25-7.15 (m, 3H), 7.13-7.05 (m, 2H), 4.45-4.25 (m, 1H), 3.62-3.48 (m, 2H), 3.00-2.86 (m, 2H), 2.85-2.65 (m, 2H), 2.06-1.92 (m,1H). MS (LRFAB): calc. 522, found 523 (M+H)+.

EXAMPLE 178

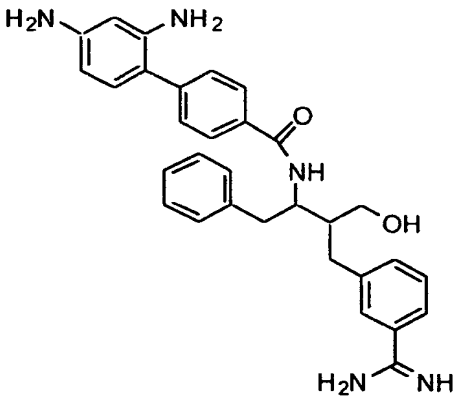
Compound 178



^{1}H NMR 300 MHz, d6 DMSO,9.23(d,4H,J=6 Hz), 8.28(d,1H,J=10 Hz),7.77(d,2H,J=10 Hz), 7.71-7.42(m,8H),7.22-7.12(m,4H), 7.10-7.01(m,3H), 4.45-4.25(m,1H), 3.65-3.45(m,2H), 3.05-2.87(m,2H), 2.85-2.65(m,2H), 2.05-1.95(m,1H). MS (LRFAB): calc'd 492, found 493 (M+H)+.

EXAMPLE 179

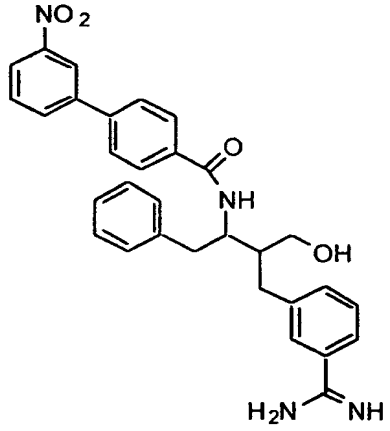
Compound 179



^{1}H NMR 300 MHz, d6 DMSO, 9.38-9.21(m,4H), 8.28(d,1H,J=10 Hz), 8.16(d,1H,J=10 Hz), 7.70-7.45(m,5H), 7.42(d,2H,J=7 Hz), 7.23(s,1H), 7.21-7.03(m,8H), 4.48-4.23(m,1H), 3.64-3.40(m,2H), 3.10-2.85(m,2H), 2.84-2.62(m,2H), 2.03-1.87(m,1H). MS (LRFAB): calc'd 507, found 508 (M+H)+.

EXAMPLE 180

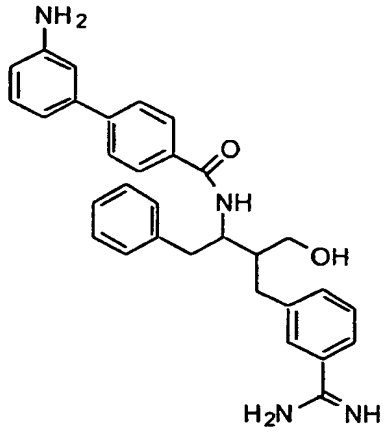
Compound 180



^{1}H NMR 300 MHz, d6 DMSO, 9.23 (s, 2H), 8.95 (s, 2H), 8.45 (s, 1H), 8.32 (d, 1H, J=8.4 Hz), 8.24 (d, 1H, J=8.4 Hz), 8.18 (d, 1H, J=7.2 Hz), 7.86 (br.s, 4H), 7.83-7.73 (m, 1H), 7.63-7.43 (m, 4H), 7.25-7.16 (m , 4H), 7.14-7.05 (m, 1H), 4.45-4.30 (m, 1H), 3.63-3.48 (m, 2H), 3.02-2.88 (m, 2H), 2.87-2.65 (m, 2H), 2.08-1.93 (m, 1H). MS(LRFAB): calc'd 522, found 523 (M+H)+.

EXAMPLE 181

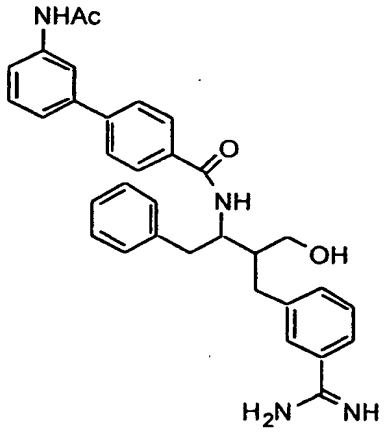
Compound 181



^{1}H NMR 300 MHz, d6 DMSO, 9.25 (s, 2H), 9.19 (s, 2H), 8.30 (d, 1H, J=9.6 Hz), 7.82 (s, 1H), 7.82 (d, 2H ,J=7.2 Hz), 7.66 (d, 2H, J=7.2 Hz), 7.63-7.45 (m, 4H), 7.38-7.27 (m, 1H), 7.25-7.13 (m , 6H), 7.13-7.05 (m, 1H), 6.93 (d, 1H, J=8.4 Hz), 4.43-4.28 (m, 1H), 3.65-3.45 (m, 2H), 3.05-2.86 (m, 2H), 2.83-2.68 (m, 2H), 2.08-1.92 (m, 1H). MS(LRFAB): calc'd 492, found 493 (M+H)+.

EXAMPLE 182

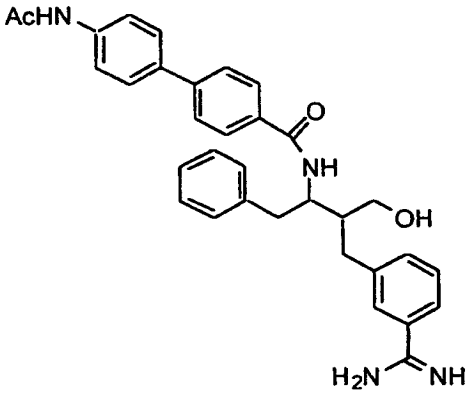
Compound 182



^{1}H NMR 300 MHz, d6 DMSO, 9.22(s,2H), 9.07(s,2H), 8.38(d,1H,J=10 Hz), 7.93(s,1H), 7.83(d,2H,J=7 Hz), 7.65(d,2H,J=7 Hz), 7.62-7.45(m,5H), 7.42-7.28(m,2H), 7.25-7.16(m,4H), 7.13-7.07(m,1H), 4.45-4.28(m,1H), 3.63-3.53(m,2H), 3.05-2.87(m,2H), 2.85-2.68(m,2H), 2.03(s,3H), 2.02-1.93(m,1H). MS(LRFAB): calc'd 534, found 535 (M+H)+.

EXAMPLE 183

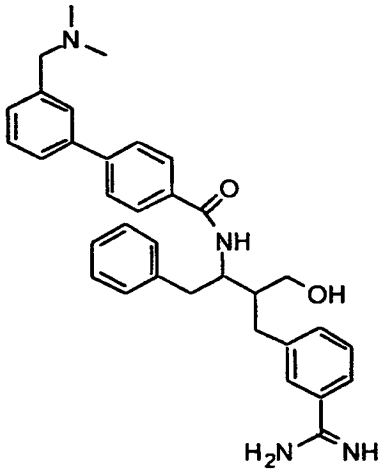
Compound 183



^{1}H NMR 300 MHz, d6 DMSO, 10.05(s,1H),9.23(s,2H), 9.10(s,2H), 8.25(d,1H,J=10 Hz), 7.78(d,2H,J=7 Hz),7.73-7.40(m,10H), 7.21-7.13(m,4H), 7.13-7.05(m,1H), 4.43-4.25(m,1H), 3.63-3.45(m,2H), 3.03-2.85(m,2H), 2.83-2.68(m,2H), 2.04(s,3H), 2.01-1.93(m,1H). MS(LRFAB): calc'd 534, found 535 (M+H)+.

EXAMPLE 184

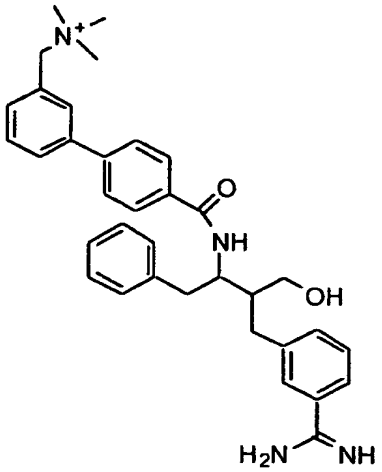
Compound 184



^{1}H NMR: 8.5 (d, 1H, J=7.0 Hz), 7.8-8.0 (m, 6H), 7.4-7.7 (M, 6H), 7.1-7.3 (m, 5H) 4.6 (m, 3H),4.1 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.7 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 2H, J=9.0 Hz), 2.9 (s, 6H), 2.0 (m, 1H). Mass Spec M+H calc 535.3, found 535.

EXAMPLE 185

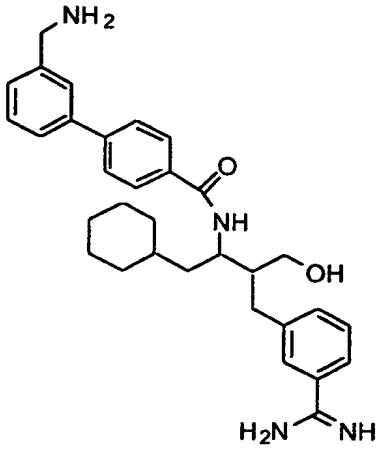
Compound 185



^{1}H NMR: 8.5 (d, 1H, J=7.0 Hz), 7.8-8.0 (m, 6H), 7.4-7.7 (M, 6H), 7.1-7.3 (m,5H) 4.6 (m,3H), 4.0 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.6 (dd, 1H, J=6.0 Hz,10.0 Hz), 3.2 (s, 9H), 3.0 (d, 2H, J=9.0 Hz), 2.9 (d, 2H, J=9.0 Hz), 2.0 (m, 1H). Mass Spec M+H calc 549.3, found 549.

EXAMPLE 186

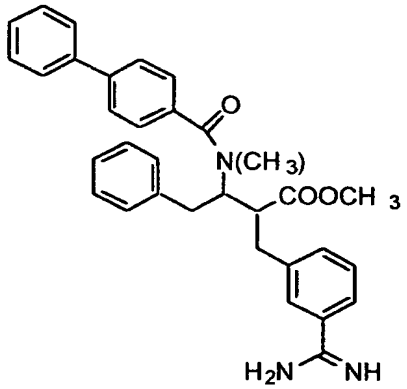
Compound 186



^{1}H NMR (300 MHz, d6 DMSO), δ 9.30-9.11 (m, 3H), 8.31 (br.s, 2H), 8.15 (d, 1H, J=8.4 Hz), 7.93 (d, 2H, J=7.2 Hz), 7.86-7.68 (m, 2H), 7.64-7.48 (m, 6H), 4.30-4.15 (m,1H), 4.14-4.04 (m, 2H), 2.75 (d, 2H, J=6.0 Hz), 1.95-1.82 (m, 1H), 1.80-1.68 (m, 2H), 1.65-1.46 (m, 5H), 1.42-1.32 (m, 1H), 1.31-1.15(m, 1H), 1.13-0.93 (m, 2H), 0.92-0.65 (m, 4H). MS, LRFAB, calc'd. 512, found 513 (M+H)+.

EXAMPLE 187

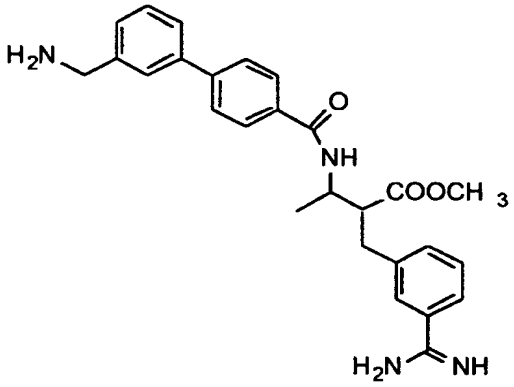
Compound 187



^{1}H NMR: 9.0 (s, 1H), 8.5 (d, 1H, J=9.0 Hz), 7.9 (d, 2H, J=9.0 Hz), 7.6-7.8 (m, 4H), 7.3-7.5 (m, 6H), 7.2-7.1 (m, 6H), 3.5 (s, 3H), 3.1 (s, 3H), 3.0 (d, 2H, J=8.0 Hz), 2.9 (d, 2H, J=8.0 Hz). M.S. Cal'd 520.1, Found 520.

EXAMPLE 188

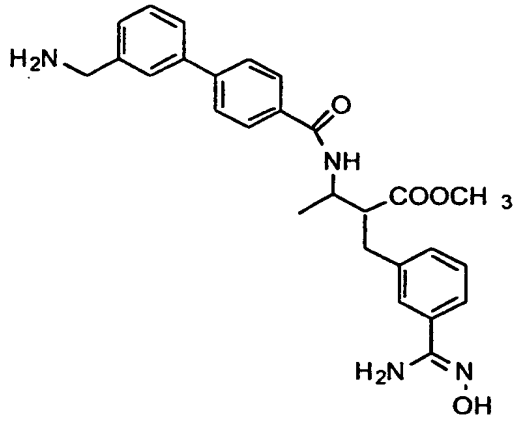
Compound 188



^{1}H NMR: 9.4 (d, 1H, J=12.0 Hz), 8.6 (d, 1H, J=10.0 Hz), 8.1 (d, 2H, J=10.0 Hz), 7.9-8.1 (m, 4H), 7.6-7.8 (m, 6H), 4.7 (m, 1H) 4,4 (d, 2H, J=9.0 Hz), 3.7 (s, 3H), 3.1-3.4 (m, 4H), 1.6 (d, 3H,J=9.0 Hz). Mass Spec M+H calc 459.2 found 459.

EXAMPLE 189

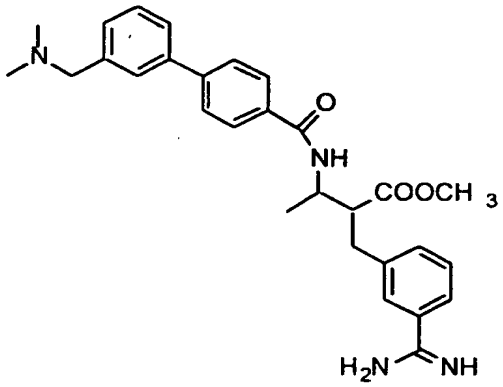
Compound 189



^{1}H NMR: 9.4 (d, 1H, J=12.0 Hz), 8.0 (d, 1H, J=10.0 Hz), 8.1 (d, 2H, J=10.0 Hz), 7.7-7.9 (m,4H), 7.4-7.6 (m, 6H), 4.5 (m, 1H), 4.2 (d,2H, J=9.0 Hz), 3.6 (s, 3H), 3.0-3.2 (m, 3H), 1.6 (d, 3H,J=9.0 Hz). Mass Spec M+H calc 475.1, found 475.

EXAMPLE 190

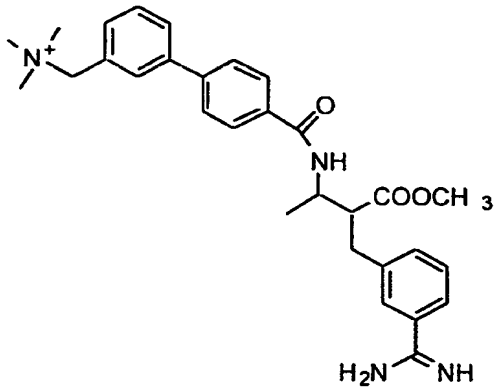
Compound 190



^{1}H NMR: 8.4 (d, 1H, J=9.0 Hz), 7.9 (d, 2H, J=10.0 Hz), 7.7-7.9 (m,4H), 7.4-7.6 (m, 6H), 4.6 (m,H), 4.5 (s,2H), 3.6 (s, 3H), 3.1-3.2 (m, 3H), 2.9 (s,6H), 1.3 (d, 3H,J=9.0 Hz). Mass Spec M+H calc 459.2 found 459.

EXAMPLE 191

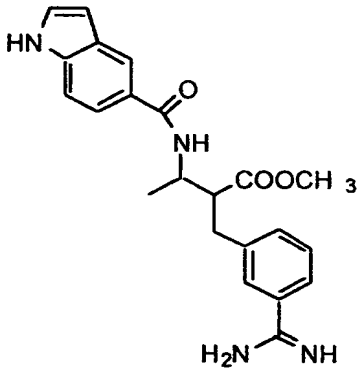
Compound 191



^{1}H NMR: 9.3 (d, 1H, J=9.0 Hz), 9.1 (d, 1H, J=9.0 Hz), 8.4 (d, 1H, J=10.0 Hz), 7.7-8.0 (m,4H), 7.3-7.6 (m, 5H), 4.6 (s, 2H), 4,4 (m, 1H), 3.5 (s, 3H), 3.1 (s,9H), 2.9-3.1 (m, 3H), 1.6 (d, 3H,J=9.0 Hz). Mass Spec M+H calc 501.1 found 501.

EXAMPLE 192

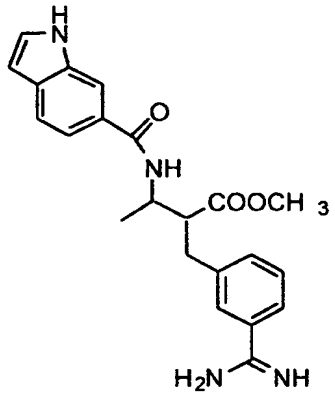
Compound 192



M.S., APCI Cal'd 392, Found 393 $(M+H)^+$.

EXAMPLE 193

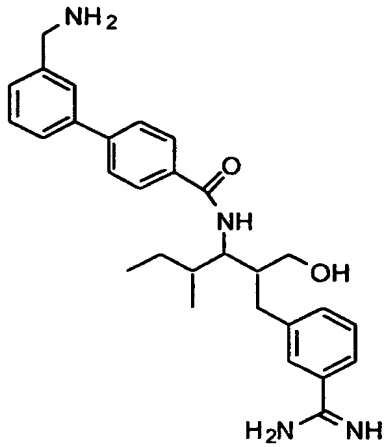
Compound 193



M.S., APCI Cal'd 392, Found 393 $(M+H)^+$.

EXAMPLE 194

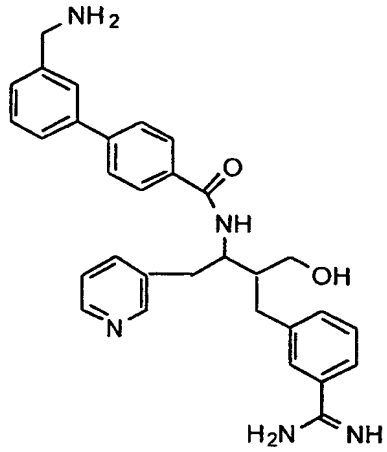
Compound 194



^{1}H NMR: 9.4 (d, 1H, J=12.0 Hz), 8.6 (d, 1H, J=10.0 Hz), 8.0 (d, 2H, J=9.0 Hz), 7.7 (d, 2H, J=9.0 Hz) , 7.3-7.6 (m, 6H), 7.0-7.2 (m,2H), 4.2 (m,3H), 4.0 (dd, 1H, (J=6.0 Hz, 10.0 Hz), 3.6 (dd, 1H, (J=6.0 Hz,10.0 Hz), 3.0 (d, 2H, J=8.0 Hz), 2.0 (m, 1H), 1.6 (m,H) 1.1-1.3 (m, 8H). Mass Spec M+H calc 473.1, found 473.

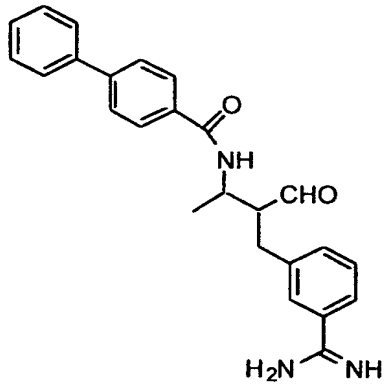
EXAMPLE 195

Compound 195



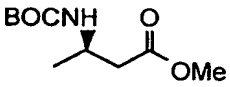
EXAMPLE 196

Compound 196



EXAMPLE 197

Compound 197

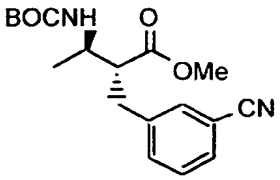


To a stirred solution of the acetic acid salt of (R)-3-aminobutyric acid methyl ester (8.9g; 50 mmol) and triethylamine (Et_3N) (21 mL; 150 mmol) in dry methylene chloride (CH_2Cl_2) under N_2 at room temperature is added di-tert-butyl dicarbonate (BOC_2O) (21.8g; 100 mmol) dropwise. 4-Dimethylaminopyridine (DMAP) (ca. 50 mg) is then added and the mixture is allowed to stir at room temperature overnight. At this point, the mixture is washed with saturated sodium bicarbonate ($NaHCO_3$) solution. The organic layer is dried over sodium sulfate (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 20% - 40% ethyl acetate (EtOAc, or EtOAc) in hexanes)

to give Compound 197. ^{1}H NMR ($CDCl_3$, δ): 4.92 (bs, 1H), 3.96 (bm, 1H), 3.65 (s, 3H), 2.45 - 2.37 (m, 2H), 1.39 (s, 9H), 1.16 (d, J = 7.9 Hz, 3H).

EXAMPLE 198

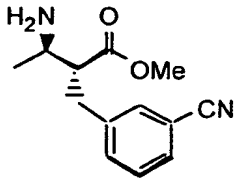
Compound 198



To a stirred solution of Compound 197 (2.00 g; 9.21 mmol) in 50 mL of dry tetrahydrofuran (THF) under nitrogen at -78°C is added lithium hexamethyldisilazane (LHMDS) solution (25.8 mL of 1.0 M solution in THF) dropwise. The mixture is then warmed up to -20 to -25°C for 30 min and then cooled back to -78°C. A solution of 3-cyanobenzyl bromide (4.51 g; 23.0 mmol) in dry THF is then added dropwise and the resulting solution allowed to warm to room temperature.. After 1 hour at room temperature, the mixture is quenched with saturated $NaHCO_3$ solution and most of the THF is removed in vacuo. The residue is taken up into CH_2Cl_2 and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is purified by flash chromatography (eluent = 25% ethyl acetate / Hexanes). The semi-solid residue is then triturated with 20% EtOAc / Hexanes and the white solid filtered off. The filtrate is then concentrated in vacuo to give Compound 198. ^{1}H NMR ($CDCl_3$, δ): 7.25 - 7.50 (m, 4H), 5.21 (bd, 1H), 3.88 (m, 1H), 3.60 (s, 3H), 3.07 - 2.73 (m, 3H), 1.48 (s, 9H), 1.14 (d, J = 7.9 Hz, 3H).

EXAMPLE 199

Compound 199

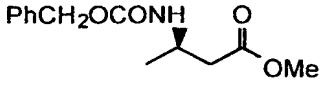


To a stirred solution of Compound 198 (4.20g; 12.7 mmol) in 10 mL of CH_2Cl_2 under N_2 at room temperature is added 20 mL of trifluoroacetic acid. The mixture is allowed to stir overnight at room temperature and then concentrated *in vacuo* to give 4.20g of Compound 199 as the trifluoroacetic acid (TFA) salt. ^{1}H NMR (DMSO-d_6, δ): 8.07 (bs, 1H), 7.73 - 7.43 (M, 4H), 3.50 (S, 3H), 3.51 (M, 1H), 3.05 - 2.82 (M, 3H), 1.23 (D, J = 7.9 HZ, 3H).

Alternatively, compound 4 may be prepared as outlined below:

EXAMPLE 200

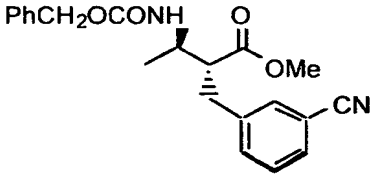
Compound 200



To a stirred solution of D-3-aminobutyric acid methyl ester (6.98 g; 39.4 mmol) acetic acid salt in 40 mL of CH_2Cl_2 is added sat. $NaHCO_3$ solution (40 mL). Benzyl chloroformate (9.0 mL; 63 mmol) is then added dropwise and the mixture allowed to stir vigorously at room temperature. After 3 hours, the organic layer is separated and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed (eluent = 10% EtOAc / $CHCl_3$) to give Compound 200. ^1H NMR ($CDCl_3$, δ): 7.40 - 7.22 (m, 5H), 5.25 (m, 1H), 5.08 (s, 2H), 4.11 (m, 1H), 3.65 (s, 3H), 2.53 (d, J = 7.0 Hz, 2H), 1.23 (d, J = 7.9 Hz, 3H).

EXAMPLE 201

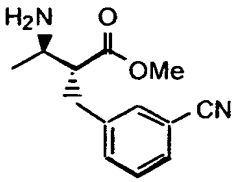
Compound 201



To a stirred solution of Compound 200 (3.45 g; 13.71 mmol) in 20 mL of dry THF under N_2 at -78°C is added LHMDS solution (41.2 mL of 1.0 M solution) dropwise. The mixture is then warmed up to -20°C for 30 minutes and then cooled back to -78°C. A solution of 3-cyanobenzyl bromide (4.51 g; 23.0 mmol) in dry THF is then added dropwise and the resulting solution allowed to warm to room temperature. After 1 hour at room temperature, the mixture is quenched with saturated $NaHCO_3$ solution and most of the THF is removed in vacuo. The residue is taken up into CH_2Cl_2 and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is purified by flash chromatography (eluent = 30% EtOAc / Hexanes). The semi-solid residue is then triturated with 20% EtOAc / Hexanes and the white solid filtered off. The filtrate is then concentrated in vacuo to Compound 201. ^1H NMR ($CDCl_3$, δ) 7.20 - 7.65 (m, 9H), 5.57 (bd, 1H), 5.12 (s, 2H), 3.97 (m, 1H), 3.60 (s, 3H), 3.07 - 2.75 (m, 3H), 1.16 (d, J = 7.9 Hz, 3H).

EXAMPLE 202

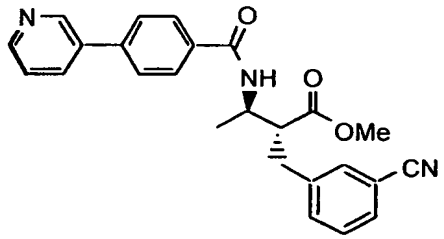
Compound 199



To a stirred solution of Compound 201 (2.6 g; 7.1 mmol) in 25 mL of ethanol (EtOH) is added 520 mg of 10% Pd / C. The mixture is stirred under 1 atm of hydrogen for 3 hours at room temperature. The mixture is then filtered through a bed of celite to remove the catalyst. The filtrate is then concentrated in vacuo to give 1.45 g of Compound 201.

EXAMPLE 203

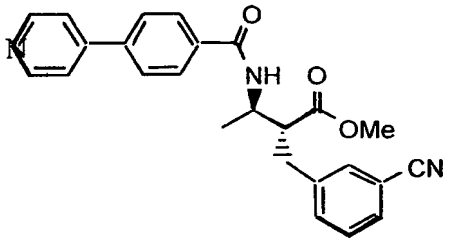
Compound 203



3'-pyridyl-4-phenyl carbonyl chloride (Compound 228, prepared as in Example 228) (384 mg; 1.8 mmol) is added in one portion to a solution of Compound 199 TFA salt (373 mg; 1.6 mmol) and Et_3N (0.67 mL; 4.8 mmol) in 5.0 mL of absolute EtOH under N_2 at room temperature. The mixture is allowed to stir overnight at room temperature. The solvent is then removed *in vacuo* and the crude product is purified by chromatography on silica gel (eluent = 70% EtOAc / Hexanes) to provide Compound 203. ^1H NMR ($CDCl_3$, δ): 8.88 (m, 1H), 8.63 (m, 1H), 7.85 - 8.00 (m, 7.70 (m, 2H), 7.57 - 7.33 (m, 6H), 4.51 (m, 1H), 3.65 (s, 3H), 3.10 - 2.82 (m, 3H), 1.28 (d, J = 7.9 Hz, 3H).

EXAMPLE 204

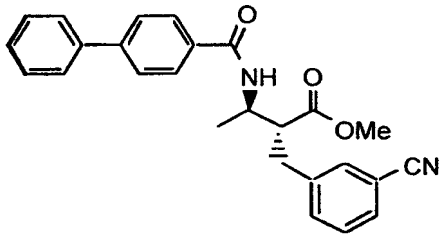
Compound 204



Acylation of Compound 199 according to the procedure of Example 203, substituting Compound 228 with 4'-pyridyl-4-phenylcarbonyl chloride (Compound 231, prepared as in Example 231) provides, after workup and chromatography, Compound 204. ^{1}H NMR ($CDCl_3$, δ): 8.70 (m, 2H), 8.02 - 7.65 (m, 4H), 7.57 - 7.32 (m, 7H), 4.50 (m, 1H), 3.68 (s, 3H), 3.10 - 2.83 (M, 3H), 1.30 (d, J = 7.9 Hz, 3H).

EXAMPLE 205

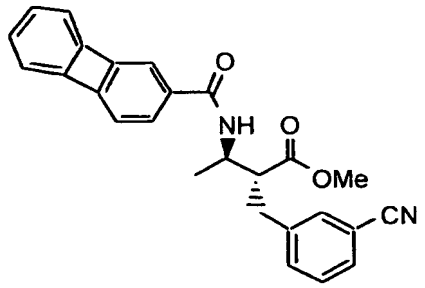
Compound 205



Acylation of Compound 199 according to Example 203, in CH_2Cl_2 rather than absolute EtOH, and substituting 3'-pyridyl-4-phenylcarbonyl chloride with 4-biphenylcarbonyl chloride provides, after workup and chromatography, Compound 205. ^{1}H NMR ($CDCl_3$, δ): 7.93 (m, 2H), 7.73 - 7.30 (m, 12H), 4.50 (m, 1H), 3.66 (s, 3H), 3.10 - 2.83 (m, 3H), 1.26 (d, J = 7.9 Hz, 3H).

\EXAMPLE 206

Compound 206

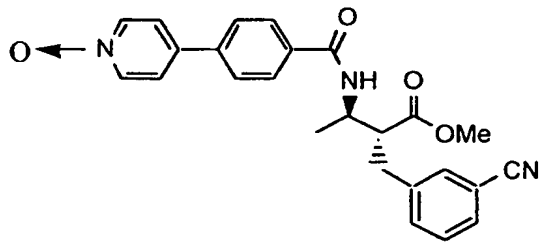


Acylation of Compound 199 according to Example 203 substituting 3'-pyridyl-4-phenylcarbonyl chloride with 2-biphenylenecarbonyl chloride provides, after workup and chromatography, Compound

206. ^{1}H NMR ($CDCl_3$, δ): 7.55 - 7.27 (m, 5H), 7.07 (m, 2H), 6.85 - 6.66 (m, 5H), 4.44 (m, 1H), 3.65 (s, 3H), 3.05 - 2.80 (m, 3H), 1.23 (d, J = 7.9 Hz, 3H).

EXAMPLE 207

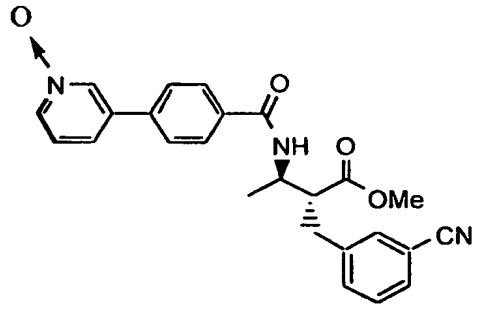
Compound 207



m-Chloroperbenzoic acid (mCPBA) (381 mg; 2.21 mmol) is added to a solution of Compound 204 (608 mg; 1.47 mmol) in 10 mL of CH_2Cl_2 under N_2 at room temperature. The resulting mixture is allowed to stir overnight at room temperature. At this point, the mixture is diluted with CH_2Cl_2 and washed with 5% Na_2CO_3 solution. The organic layer is dried (Na_2SO_4), filtered and concentrated to give Compound 207. MS: $M^{+\cdot}$ + H^+ (Calc.) = 430 ; Found (FAB) = 430.

EXAMPLE 208

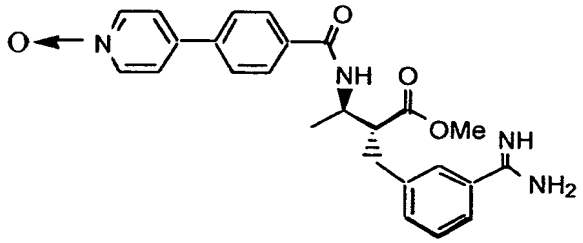
Compound 208



m-Chloroperbenzoic acid (124 mg; 0.72 mmol) is added to a solution of Compound 203 (150 mg; 0.36 mmol) in 10 mL of CH_2Cl_2 under N_2 at room temperature. The resulting mixture is allowed to stir overnight at room temperature. At this point, the mixture is diluted with CH_2Cl_2 and washed with 5% Na_2CO_3 solution. The organic layer is dried (Na_2SO_4), filtered and concentrated to give Compound 208. ^{1}H NMR ($CDCl_3$, δ): 8.57 (m, 1H), 8.30 (m, 1H), 7.95 (m, 2H), 7.73 - 7.35 (m, 9H), 4.50 (m, 1H), 3.68 (s, 3H), 3.07 - 2.85 (m, 3H), 1.20 (d, J = 7.9 Hz, 3H).

EXAMPLE 209

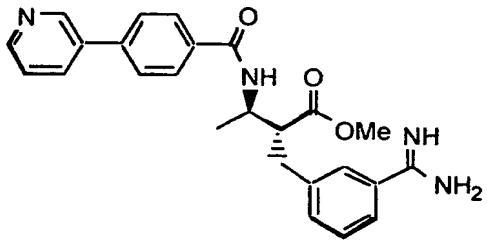
Compound 209



Hydrogen chloride gas (HCl (g)) is bubbled into a solution of Compound 207 (480 mg) in 5.0 mL of dry methanol (MeOH) containing 3Å molecular sieves (pellets, ca. 50 mg) for about 2 minutes at room temperature. The mixture is allowed to stir overnight at room temperature and then concentrated *in vacuo*. A solution of ammonia (NH_3) in MeOH (5.0 mL of 7N solution) is added and the mixture refluxed for 1 hour. The solvent is then removed *in vacuo* and the crude product purified by RPHPLC (CH_3CN / H_2O, 0.1% TFA, gradient:10% to 100% CH_3CN and the fractions containing product are lyophilized to give Compound 209. ^1H NMR (MeOH-d4, δ): 8.42 (m, 2H), 8.00 - 7.85 (m, 6H), 7.68 - 7.47 (m, 4H), 4.47 (m, 1H), 3.60 (s, 3H), 3.18 - 3.00 (m, 3H), 1.33 (d, J = 7.9 Hz, 3H). MS: $M^{+\cdot} + H^+$ (Calc.) = 447 ; Found (FAB) = 447.

EXAMPLE 210

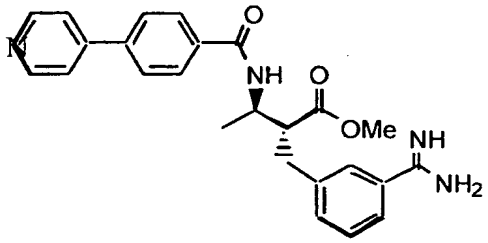
Compound 210



Treatment of Compound 203 in a similar manner as in Example 209 provides, after purification by RPHPLC, Compound 210. ^1H NMR (DMSO-d6, δ): 9.36 (m, 3H), 8.50 - 8.27 (m, 2H), 8.00 - 7.80 (m, 3H), 7.80 - 7.40 (m, 4H), 4.40 (m, 1H), 3.49 (s, 3H), 3.13 - 2.81 (m, 3H), 1.25 (d, J = 7.9 Hz, 3H). MS: $M^{+\cdot} + H^+$ (Calc.) = 431 ; Found (FAB) = 431

EXAMPLE 211

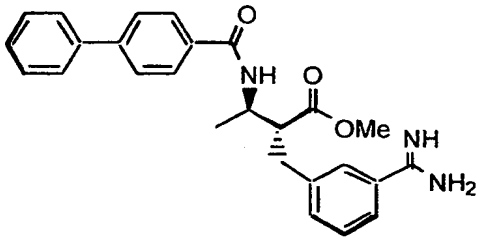
Compound 211



Treatment of Compound 204 in a similar manner as in Example 209 provides, after purification by RPHPLC, Compound 211.

EXAMPLE 216

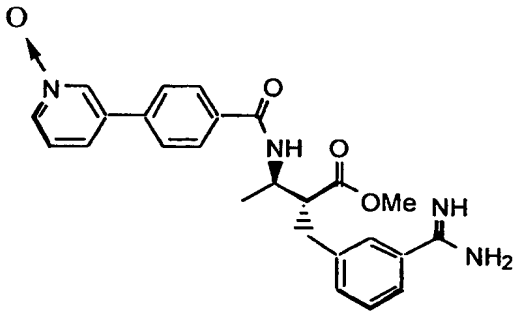
Compound 216



Treatment of Compound 205 in a similar manner as in Example 209 above provides, after purification by RPHPLC, compound 216. ^{1}H NMR (DMSO-d$_6$, δ): 9.30 (s, 1H), 9.00 (s, 1H), 8.40 (m, 1H), 8.05 - 7.40 (m, 12 H), 4.46 (m, 1H), 3.56 (s, 3H), 3.20 -2.97 (m, 3H), 1.28 (d, J = 7.9 Hz, 3H). MS: $M^{+\cdot} + H^+$ (Calc.) = 430 ; Found (FAB) = 430.

EXAMPLE 217

Compound 217

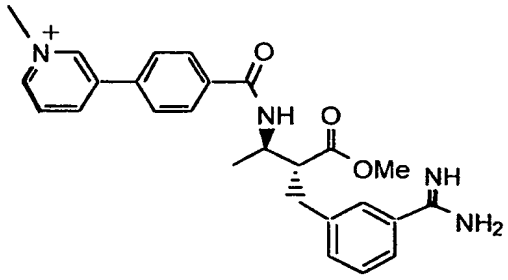


Treatment of Compound 208 in a similar manner as in Example 209 above provides, after purification by RPHPLC, Compound 217. ^{1}H NMR (MeOH-d4, δ): 8.67 (m, 1H), 8.50 - 8.35 (m, 2H),

8.00 - 7.78 (m, 5H), 7.72 - 7.48 (m, 5H), 4.47 (m, 1H), 3.60 (s, 3H), 3.16 - 3.05 (m, 3H), 1.32 (d, J = 7.9 Hz, 3H). MS: $M^{+\cdot} + H^+$ (Calc.) = 447 ; Found (FAB) = 447.

EXAMPLE 218

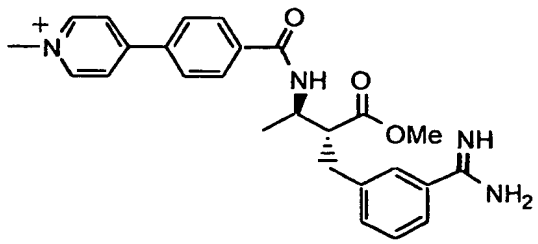
Compound 218



Hydrogen sulfide gas (H_2S) is bubbled into a solution of Compound 203 (498 mg; 1.21 mmol) in 5.0 mL of pyridine and 1.0 mL of Et_3N for ca. 2 minutes. The resulting mixture is allowed to stir overnight at room temperature and then concentrated to dryness under a stream of N_2. The residue is taken up into 5 mL of CH_2Cl_2 and 5 mL of methyl iodide is added. The mixture is refluxed for 3 hours, allowed to cool to room temperature and concentrated *in vacuo*. The residue is then taken up into 5 mL dry MeOH and NH_4OAc (300 mg) is added. The resulting mixture is refluxed for 3h and then concentrated *in vacuo*. The crude product is purified by RPHPLC (CH_3CN / H_2O, 0.1% TFA, gradient:10% to 100% CH_3CN and the fractions containing product are lyophilized to give Compound 218. ^1H NMR (MeOH-d4, δ): 9.35 (s, 1H), 8.92 (m, 2H), 8.50 (d, 1H), 8.17 (m, 1H), 8.08 - 7.92 (m, 4H), 7.66 - 7.50 (m, 4H), 4.50 (s, 3H), 4.50 (m, 1H), 3.58 (s, 3H), 3.15 - 3.02 (m, 3H), 1.34 (d, J = 7.9 Hz, 3H). MS: $M^{+\cdot}$ (Calc.) = 445 ; Found (FAB) = 445.

EXAMPLE 219

Compound 219

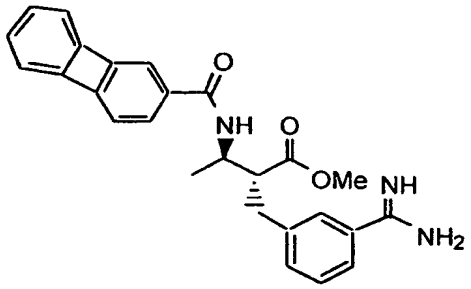


Treatment of Compound 204 in a similar manner to that of Compound 203 in EXAMPLE 218 above provides, after purification by RPHPLC, Compound 219. ^1H NMR (DMSO-d6, δ): 9.05 (m, 1H),

8.55 (m, 3H), 8.20 - 7.97 (m, 5H), 7.65 - 7.47 (m, 4H), 4.33 (s, 3H), 4.10 (m, 1H), 3.13 (s, 3H), 3.13 - 2.90 (m, 3H), 1.27 (d, J = 7.9 Hz, 3H). MS: $M^{+\cdot}$ (Calc.) = 445 ; Found (FAB) = 445.

EXAMPLE 220

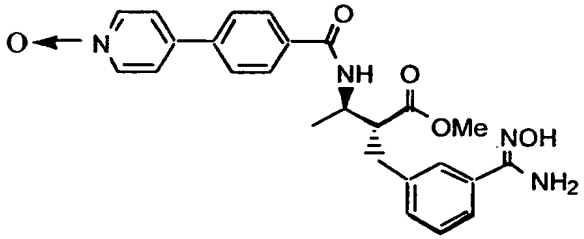
Compound 220



Treatment of Compound 206 in a similar manner to that of Compound 203 in EXAMPLE 218 above provides, after purification by RPHPLC, compound 220.

EXAMPLE 221

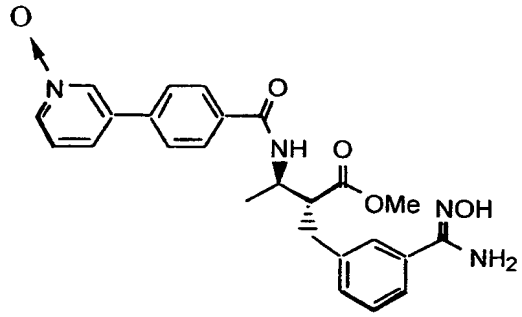
Compound 221



To a stirred solution of sodium methoxide in MeOH (12.4 mL of 0.5 M solution) is added hydroxylamine hydrochloride. Once all the solid dissolves, the solution is added to a solution of Compound 207 (530 mg; 1.24 mmol) in 5 mL of MeOH at room temperature. The resulting mixture is allowed to stir at room temperature under N_2 overnight. At this point, the solvent is removed *in vacuo* and the product purified by flash chromatography (eluent = 10% MeOH / CH_2Cl_2). The fractions containing product are concentrated *in vacuo* and the residue is then lyophilized from water to give Compound 221. ^{1}H NMR ($CDCl_3$, δ): 9.60 (s, 1H), 8.60 - 7.10 (m, 12H), 5.80 (bs, 1H), 4.40 (m, 1H), 4.45 (s, 3H), 3.15 - 2.80 (m, 3H), 1.15 (d, J = 7.9 Hz, 3H). MS: $M^{+\cdot} + H^+$ (Calc.) = 463 ; Found (FAB) = 463.

EXAMPLE 222

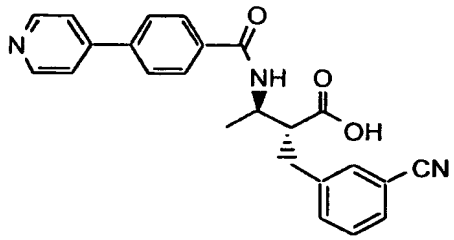
Compound 222



Treatment of Compound 208 in a similar manner to that of Compound 207 in Example 221 above provides, after purification by flash chromatography, compound 222. ^{1}H NMR (MeOH-d4, δ): 8.69 (m, 1H), 8.35 (m, 1H), 8.00 - 7.75 (m, 5H), 7.72 - 7.25 (m, 5H), 4.47 (m, 1H), 3.57 9s, 3H), 3.15 - 2.95 (m, 3H), 1.33 (d, J =- 7.9 Hz, 3H). MS: $M^{+\cdot} + H^+$(Calc.) = 463 ; Found (ion spray) = 463.

EXAMPLE 223

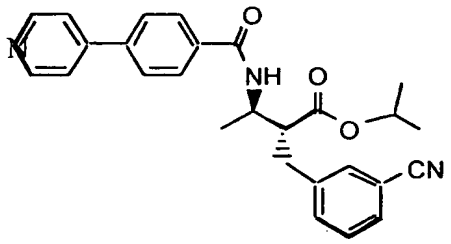
Compound 223



To a stirred solution of Compound 204 (319 mg; 0.77 mmol) in 4 mL of MeOH / THF (1 / 1) is added 1 N NaOH solution (10 mL). The resulting mixture is allowed to stir for 2 hours at room temperature and then acidified with 12 mL of 1 N HCl solution. The solid product Compound 223 is filtered off and dried *in vacuo*. ^{1}H NMR ($CDCl_3$, δ): 9.30 (bs, 1H), 8.50 (bs, 1H), 8.30 - 7.80 (m, 6H), 7.65 - 7.28 (m, 5H), 4.40 (m, 1H), 3.20 - 2.85 (m, 3H), a.33 (d, J = 7.9 Hz, 3H).

EXAMPLE 224

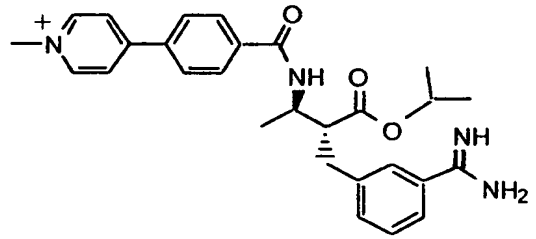
Compound 224



Triethylamine (0.11 mL; 0.77 mmol) is added dropwise to a suspension of Compound 223 in dry CH_2Cl_2 (10 mL) under N_2 at room temperature. After 10 minutes, isopropyl chloroformate (0.77 mL; 0.77 mmol) is added dropwise. After 30 minutes, DMAP (31 mg) is added and the mixture allowed to stir overnight at room temperature. At this point, the mixture is diluted with CH_2Cl_2 and washed with 1 N HCl. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is chromatographed with 40% EtOAc / hexanes followed by 70% EtOAc / hexanes to give Compound 224. MS: $M^{+\cdot}$ + H+ (Calc.) = 442 ; Found (Ion spray) = 442.

EXAMPLE 225

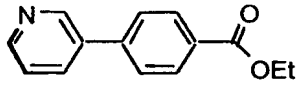
Compound 225



Treatment of Compound 224 in a similar manner to that of Compound 203 in Example 218 above provides, after purification by RPHPLC, Compound 225. ^{1}H NMR (DMSO-d_6, δ): 9.28 (m, 1H), 9.00 (m, 3H), 8.53 (m, 1H), 8.23 - 7.92 (m, 4H), 7.32 (s, 1H), 7.15 (s, 1H), 7.00 (s, 1H), 4.38 (m, 1H), 4.32 (s, 3H), 3.14 - 2.93 (m, 3H), 1.25 (m, 3H), 0.99 (m, 3H), 0.87 (m, 3H). MS: $M^{+\cdot}$ (Calc.) = 473 ; Found (FAB) = 473.

EXAMPLE 226

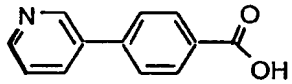
Compound 226



Ethyl-4-bromobenzoate (7.0g; 31 mmol) is dissolved in 100 mL of THF. To this solution is added $Pd(Ph_3P)_4$ (1.0g; 1.0 mmol), tetrabutylammonium bromide (592 mg; 1.8 mmol), powdered potassium hydroxide (KOH) (3.4g; 61 mmol) and diethyl-(3-pyridyl)borane (3.0g). The resulting mixture is refluxed for 2.5 hours, allowed to cool to room temperature and concentrated in vacuo. The crude product is taken up into MeOH and chromatographed (eluent = gradient, 50% EtOAc / Hexanes to 70% EtOAc / Hexanes) to give, after solvent evaporation, Compound 226. ^{1}H NMR ($CDCl_3$, δ): 8.83 (s, 1H), 8.60 (m, 1H), 8.10 (m, 2H), 7.90 - 7.30 (m, 3H), 4.34 (m, 2H), 1.37 (m, 3H).

EXAMPLE 227

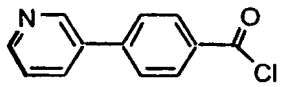
Compound 227



Sodium hydroxide solution (25.5 mL of 1.0N solution) is added dropwise to a stirred solution of Compound 226 (2.7g; 12 mmol) in 21 mL of 1 / 1 THF / MeOH at room temperature. After 3 hours, 25 mL of 1N HCl is added and the white precipitate is filtered off. The solid is dried *in vacuo*. to give Compound 227. ^{1}H NMR (DMSO-d_6, δ): 8.90 (s, 1H), 8.60 (s, 1H), 8.13 (m, 1H), 8.05 - 7.80 (m, 4H), 7.50 (m, 1H).

EXAMPLE 228

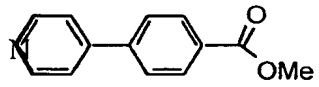
Compound 228



Thionyl chloride (5 mL) is added to 1.3 g of Compound 227. The resulting mixture is refluxed for 2 hours and then concentrated *in vacuo* to give Compound 228. MS: $M^{+\cdot}$ (Calc.) = 217 ; Found (EI) = 217.

EXAMPLE 229

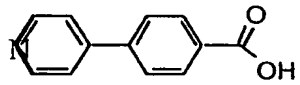
Compound 229



A mixture of methyl coumalate (10g; 65 mmol), 4-vinylpyridine (35 mL; 325 mmol) and 10% Pd / C (25g) in mesitylene (300 mL) is heated at 200°C for 30 hours. At this point, the mixture is allowed to cool and filtered through celite washing with $CHCl_3$. Most of the solvent is then removed *in vacuo* and the remaining liquid is chromatographed (eluent: Gradient, 50% EtOAc / Hex. to 70% EtOAc / Hex.) to give Compound 229. MS: $M^{+\cdot}$ (Calc.) = 213 ; Found (EI) = 213.

EXAMPLE 230

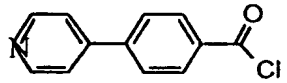
Compound 230



Treatment of Compound 229 with sodium hydroxide in THF / MeOH as in Example 227 provides Compound 230. MS: $M^{+\cdot}$ (Calc.) = 199 ; Found (EI) = 199.

EXAMPLE 231

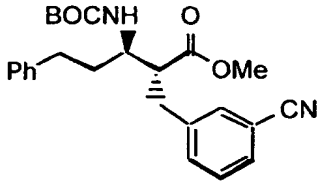
Compound 231



Treatment of Compound 230 with refluxing thionyl chloride as in Example 228 provides Compound 231. MS: $M^{+\cdot}$ (Calc.) = 217 ; Found (EI) = 217.

EXAMPLE 232

Compound 232

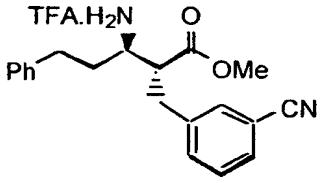


To N-BOC homophenylalanine methylester (5.57g; 18.1 mmol) in 30 mL of THF under N_2 at -78°C is added LHMDS solution dropwise (54.3 mL of 1N solution in THF). The mixture is then allowed to warm up to 0°C for 30 min and then cooled back to -78°C. A solution of 3-cyanobenzyl bromide (7.46 g; 38.0 mmol) in dry THF is then added dropwise and the resulting solution allowed to

warm to room temperature. After 1 hour at room temperature, the mixture is quenched with saturated $NaHCO_3$ solution and most of the THF is removed *in vacuo*. The residue is taken up into CH_2Cl_2 and washed with water. The organic layer is dried (Na_2SO_4), filtered and concentrated. The crude product is purified by flash chromatography (eluent = 25% EtOAc / Hexanes. The semi-solid residue is then triturated with 20% EtOAc / Hexanes and the white solid filtered off. The filtrate is then concentrated in vacuo to Compound 232. ^1H NMR ($CDCl_3$, δ): 7.82 - 7.08 ((m, 9H), 5.32 (bd, 1H), 3.84 (m, 1H), 3.60 (s, 3H), 3.06 - 2.57 (m, 5H), 1.70 (m, 2H), 1.47 (s, 9H).

EXAMPLE 233

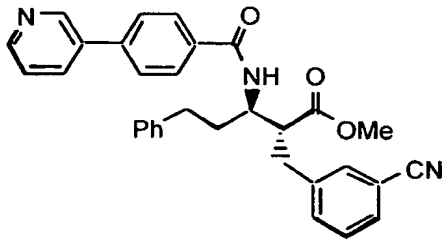
Compound 233



To a stirred solution of Compound 232 (1.42g; 3.35 mmol) in 5.0 mL of CH_2Cl_2 under N_2 at 0°C is added 3.5 mL of trifluoroacetic acid. The mixture is allowed to stir for 2 hours at room temperature and then concentrated *in vacuo* to give Compound 233 as the TFA salt. MS: $M^{+\cdot}$ (Calc.) = 322 ; Found (EI) = 322.

EXAMPLE 234

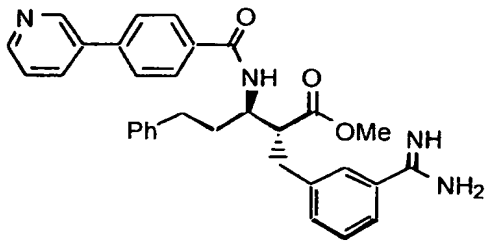
Compound 234



Acylation of Compound 233 according to Example 203 with Compound 228 provides, after workup and chromatography, Compound 234. MS: $M^{+\cdot}$ (Calc.) = 503 ; Found (EI) = 503.

EXAMPLE 235

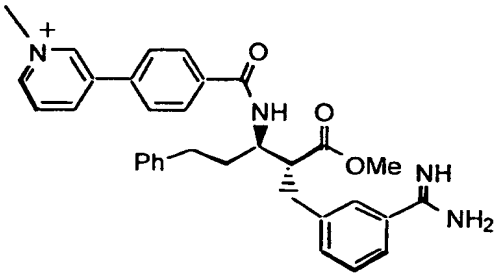
Compound 235



Treatment of Compound 234 with HCl / MeOH, then NH_4OAc in a similar manner to Compound 207 in Example 209 above provides, after purification by RPHPLC, Compound 235. MS: $M^{+\cdot} + H+$ (Calc.) = 521 ; Found (FAB) = 521.

EXAMPLE 236

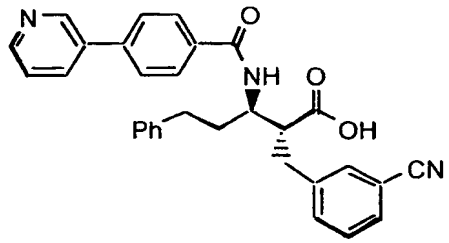
Compound 236



Treatment of Compound 234 in a similar manner to that of Compound 203 in EXAMPLE 218 above provides, after purification by RPHPLC, Compound 236. ^1H NMR (MeOH-d_4): 9.35 (s, 1H), 8.90 (m, 2H), 8.45 (m, 1H), 8.17 (m, 1H), 8.11 - 7.92 (m, 4H), 7.68 - 7.46 (m, 5H), 7.27 - 7.10 (m, 6H), 4.50 (s, 3H), 4.40 (m, 1H), 3.57 (s, 3H), 3.05 (m, 3H), 2.67 (m, 2H), 2.00 (m, 2H).

EXAMPLE 237

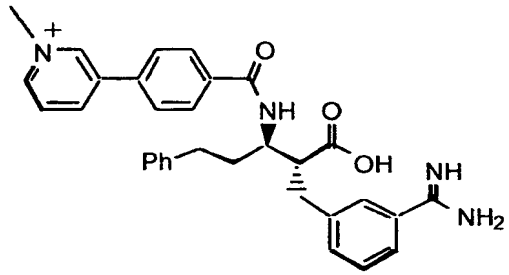
Compound 237



Hydrolysis of Compound 234 with sodium hydroxide in THF / MeOH using the procedure of Example 227 provides after workup, Compound 237. MS: $M^{+\cdot}$ + H+ (Calc.) = 490 ; Found (FAB) = 490.

EXAMPLE 238

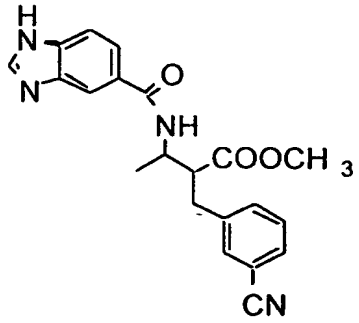
Compound 238



Treatment of Compound 237 in a similar manner to Compound 203 in Example 218 above provides, after purification by RPHPLC, Compound 238. ^{1}H NMR (MeOH-d_4): 9.38 (s, 1H), 8.90 (m, 2H), 8.47 (m, 1H), 8.17 (m, 1H), 8.11 - 7.92 (m, 4H), 7.68 - 7.46 (m, 5H), 7.26 - 7.10 (m, 6H), 4.50 (s, 3H), 4.38 (m, 1H), 3.12 - 2.97 (m,. 3H), 2.68 (m, 2H), 2.03 (m, 2H).

EXAMPLE 239

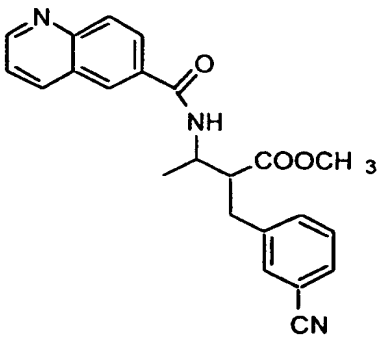
Compound 239



This material is prepared following the procedure described for compound 123 and substituting benzimidazole-5-carboxyic acid for 99.

EXAMPLE 240

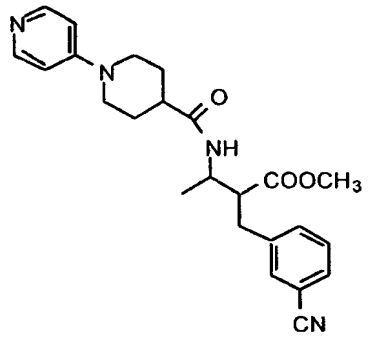
Compound 240



This material is prepared following the procedure described for compound 123 and substituting quinoline-7-carboxylic acid for 99.

EXAMPLE 241

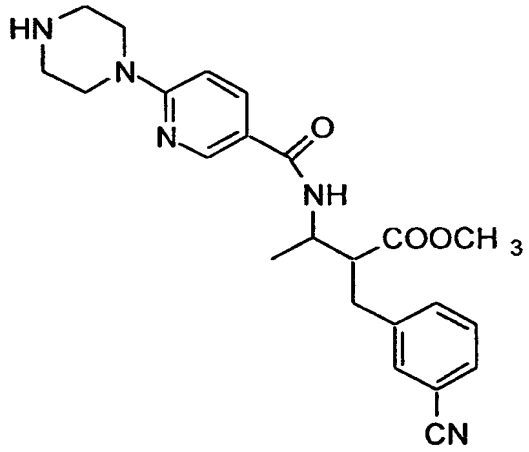
Compound 241



This material is prepared following the procedure described for compound 123 and substituting N-(4-pyridyl)-piperidine-4-carboxylic acid for 99.

EXAMPLE 242

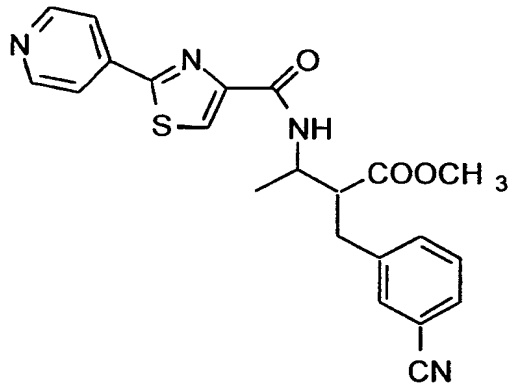
Compound 242



This material is prepared following the procedure described for compound 123 and substituting 2-(1-piperazinyl)-pyridine-5-carboxylic acid for 99.

EXAMPLE 243

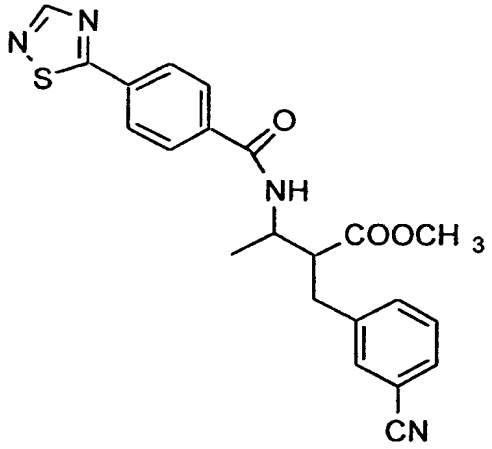
Compound 243



This material is prepared following the procedure described for compound 123 and substituting 2-(4-pyridinyl)-1,3-thiazole-4-carboxylic acid for 99.

EXAMPLE 244

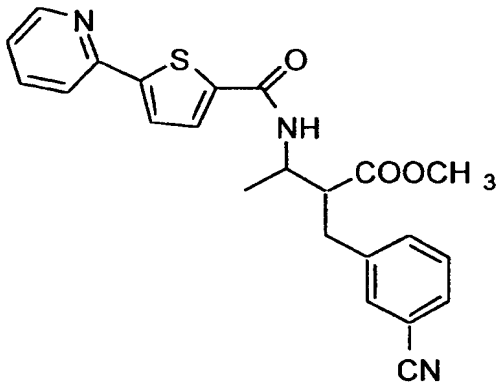
Compound 244



This material is prepared following the procedure described for compound 123 and substituting 4-(5-(1,2,4-thiadiazolyl))benzoic acid for 99.

EXAMPLE 245

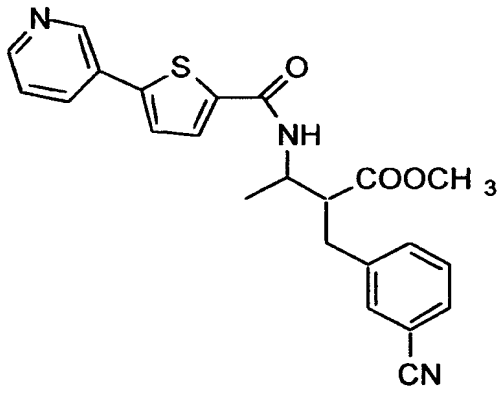
Compound 245



This material is prepared following the procedure described for compound 123 and substituting 2-(2-pyridyl)thiophene-5-carboxylic acid for 99.

EXAMPLE 246

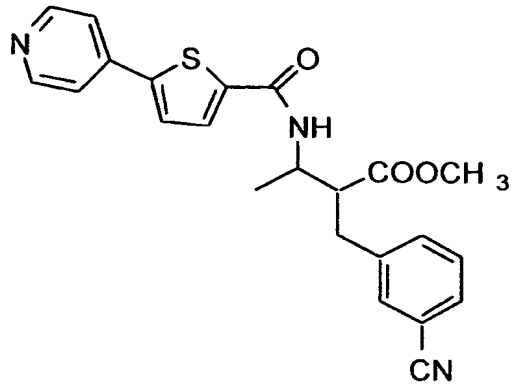
Compound 246



This material is prepared following the procedure described for compound 123 and substituting 2-(3-pyridyl)thiophene-5-carboxylic acid for 99.

EXAMPLE 247

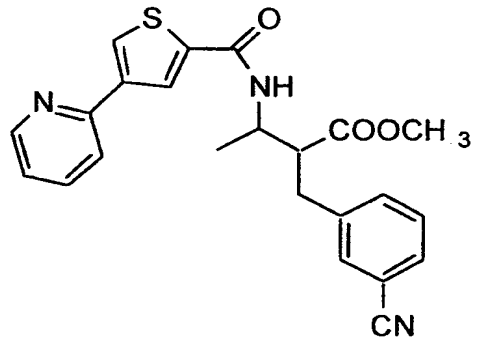
Compound 247



This material is prepared following the procedure described for compound 123 and substituting 2-(4-pyridyl)thiophene-5-carboxylic acid for 99.

EXAMPLE 248

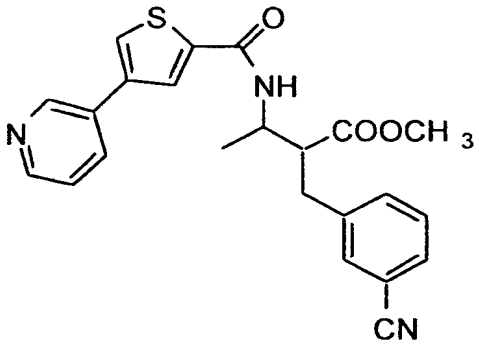
Compound 248



This material is prepared following the procedure described for compound 123 and substituting 3-(2-pyridyl)thiophene-5-carboxylic acid for 99.

EXAMPLE 249

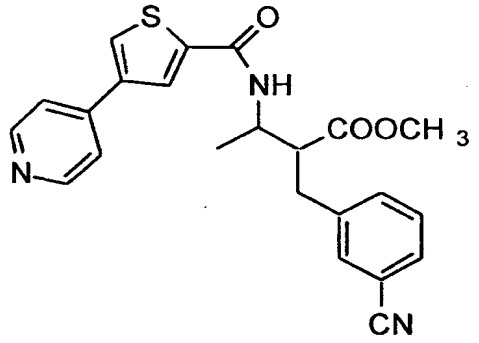
Compound 249



This material is prepared following the procedure described for compound 123 and substituting 3-(3-pyridyl)thiophene-5-carboxylic acid for 99.

EXAMPLE 250

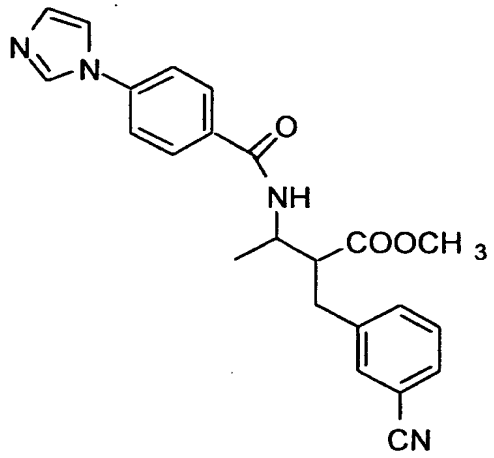
Compound 250



This material is prepared following the procedure described for compound 123 and substituting 3-(4-pyridyl)thiophene-5-carboxylic acid for 99.

EXAMPLE 251

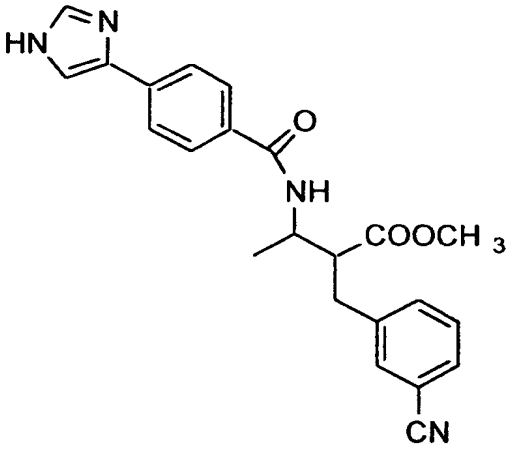
Compound 251



This material is prepared following the procedure described for compound 123 and substituting 4-(1-imidazolyl)benzoic acid for 99.

EXAMPLE 252

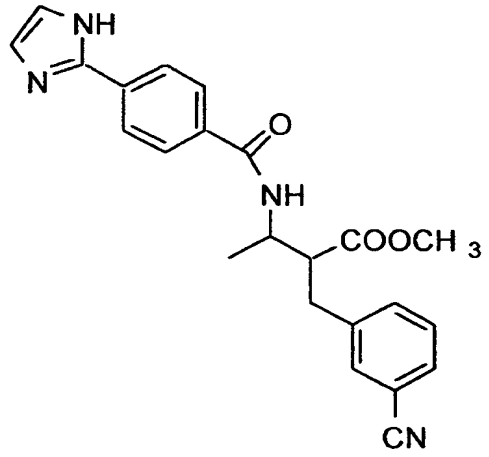
Compound 252



This material is prepared following the procedure described for compound 123 and substituting 4-(4-imidazolyl)benzoic acid for 99.

EXAMPLE 253

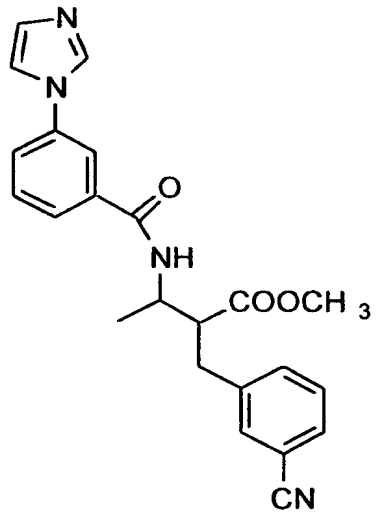
Compound 253



This material is prepared following the procedure described for compound 123 and substituting 4-(2-imidazolyl)benzoic acid for 99.

EXAMPLE 254

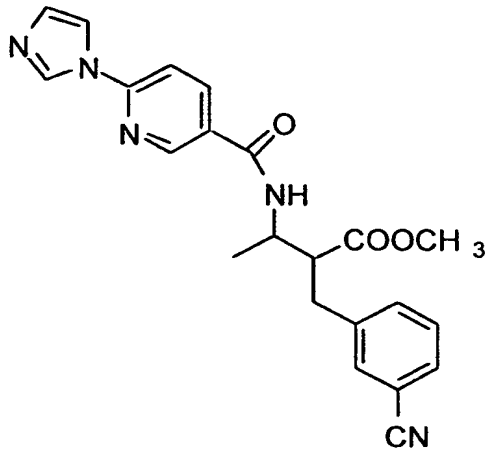
Compound 254



This material is prepared following the procedure described for compound 123 and substituting 3-(1-imidazolyl)benzoic acid for 99.

EXAMPLE 255

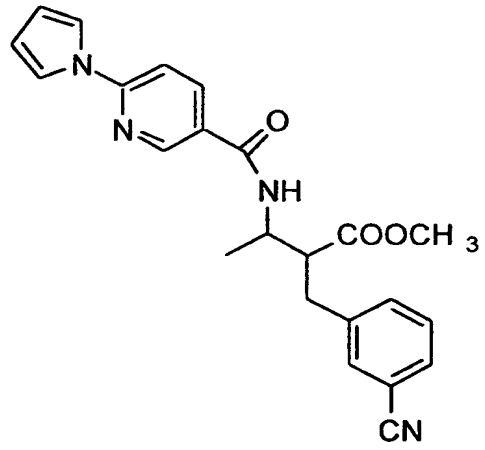
Compound 255



This material is prepared following the procedure described for compound 123 and substituting 2-(1-imidazolyl)-pyridine-5-carboxylic acid for 99.

EXAMPLE 256

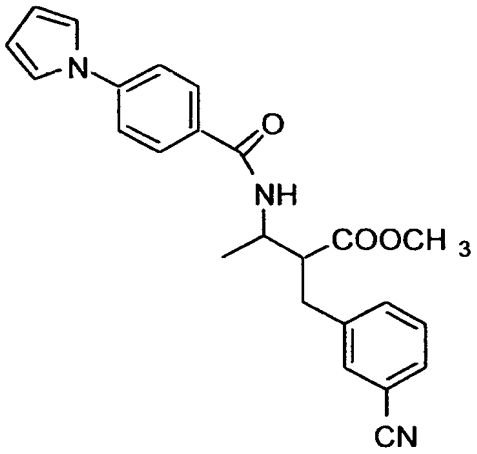
Compound 256



This material is prepared following the procedure described for compound 123 and substituting 2-(1-pyrrolyl)-pyridine-5-carboxylic acid for 99.

EXAMPLE 257

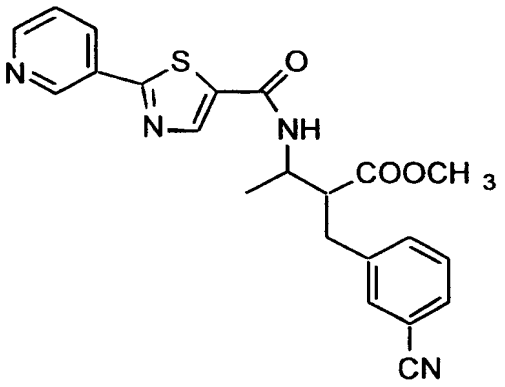
Compound 257



This material is prepared following the procedure described for compound 123 and substituting 4-(1-pyrrolyl)benzoic acid for 99.

EXAMPLE 258

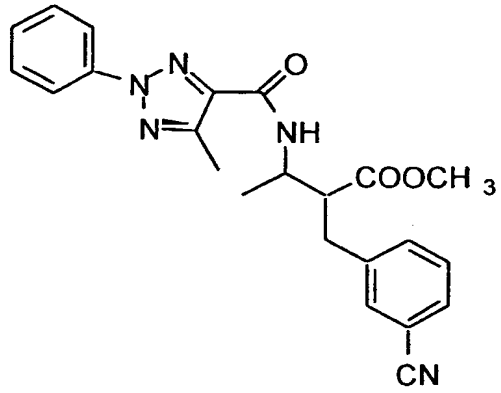
Compound 258



This material is prepared following the procedure described for compound 123 and substituting 5-(3-pyridyl)-1,3-thiazole-2-carboxylic acid for 99.

EXAMPLE 259

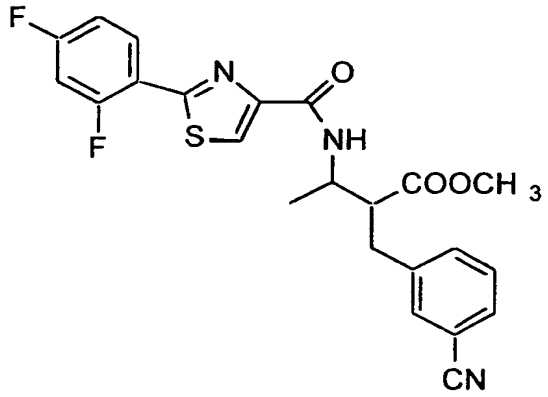
Compound 259



This material is prepared following the procedure described for compound 123 and substituting 2-phenyl-5-methyl-1,2,3-triazole-4-carboxylic acid for 99.

EXAMPLE 260

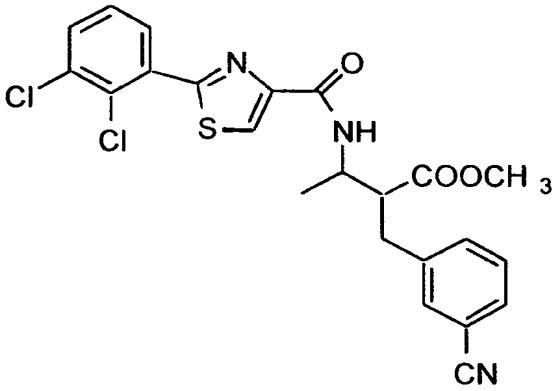
Compound 260



This material is prepared following the procedure described for compound 123 and substituting 2-(2,4-difluorophenyl)-1,3-thiazole-4-carboxylic acid for 99.

EXAMPLE 261

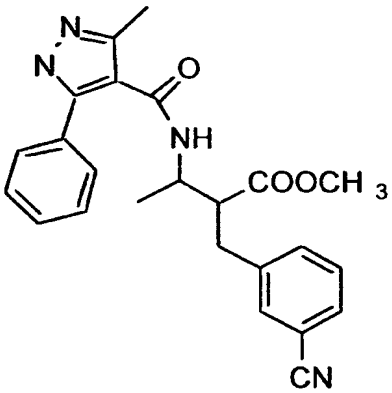
Compound 261



This material is prepared following the procedure described for compound 123 and substituting 2-(2,3-dichlorophenyl)-1,3-thiazole-4-carboxylic acid for 99.

EXAMPLE 262

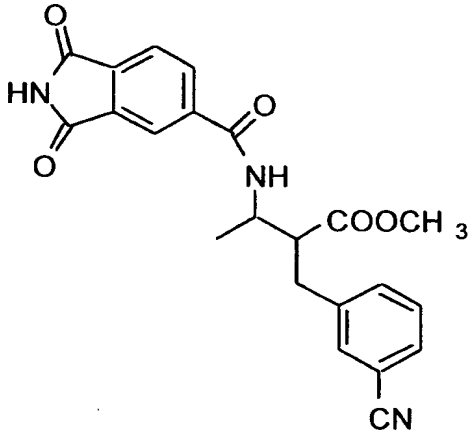
Compound 262



This material is prepared following the procedure described for compound 123 and substituting 3-phenyl-5-methyl-1,2-diazole-4-carboxylic acid for 99.

EXAMPLE 263

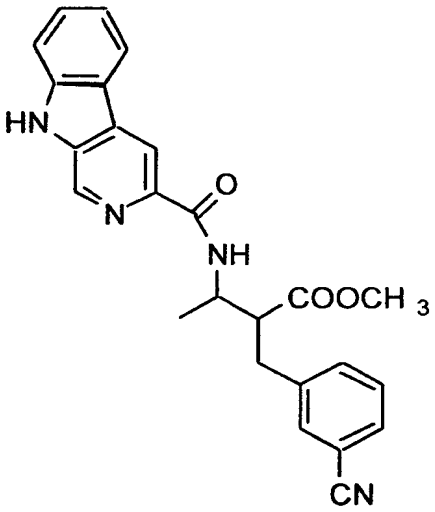
Compound 263



This material is prepared following the procedure described for compound 123 and substituting 1,2-phthalimide-4-carboxylic acid for 99.

EXAMPLE 264

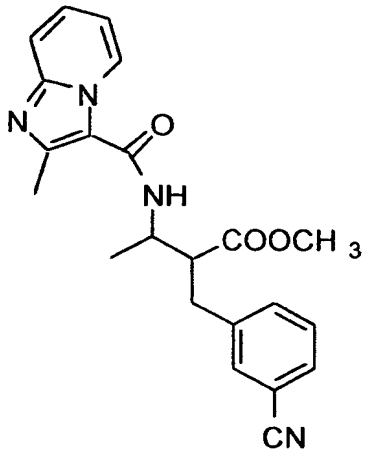
Compound 264



This material is prepared following the procedure described for compound 123 and substituting 3-aza-b-carboline-4-carboxylic acid for 99.

EXAMPLE 265

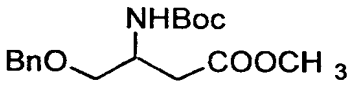
Compound 265



This material is prepared following the procedure described for compound 123 and substituting 2-methyl-1-azaindolizine-3-carboxylic acid for 99.

EXAMPLE 266

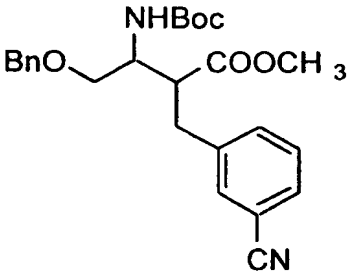
Compound 266



This material is prepared following the procedure described for compound 56 and substituting N-a-Boc-O-benzyl-D-serine.

EXAMPLE 267

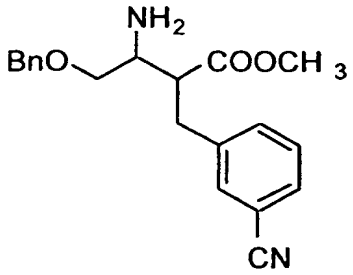
Compound 267



This material is prepared following the procedure described for compound 62 and substituting Compound 266.

EXAMPLE 268

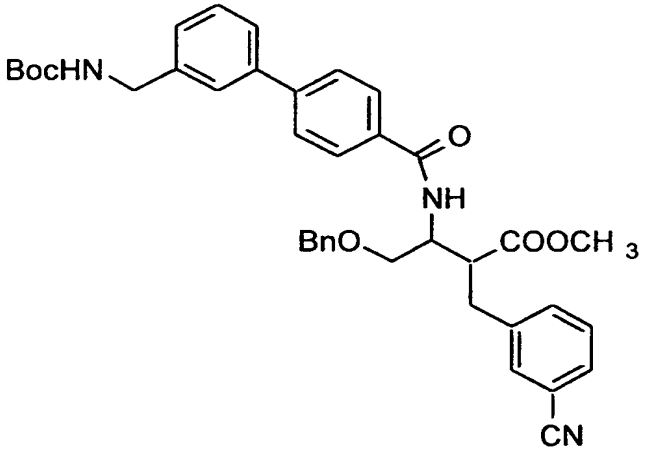
Compound 268



This material is prepared following the procedure described for compound 68 and substituting Compound 267.

EXAMPLE 269

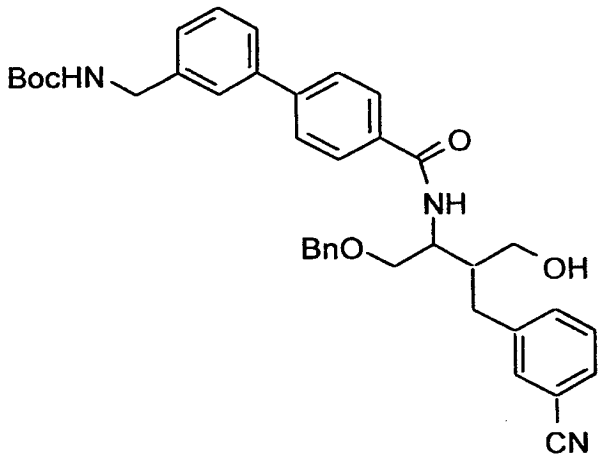
Compound 269



This material is prepared following the procedure described for compound 114 and substituting Compound 268.

EXAMPLE 270

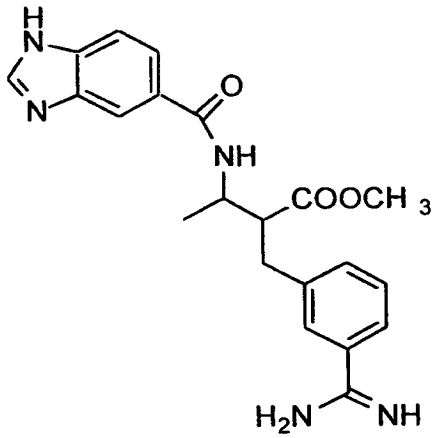
Compound 270



This material is prepared following the procedure described for compound 129 and substituting Compound 269.

EXAMPLE 271

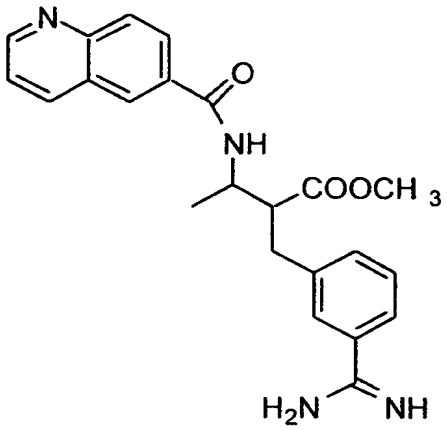
Compound 271



This material is prepared following the procedure described for compound 159a and substituting Compound 239. MS: $(M+H)^+$ 395.

EXAMPLE 272

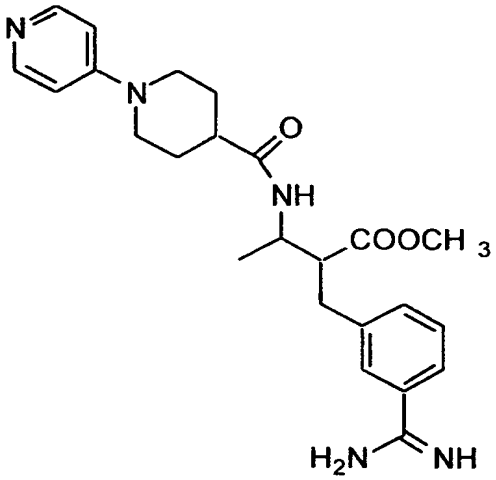
Compound 272



This material is prepared following the procedure described for compound 159a and substituting Compound 240. MS: $(M+H)^+$ 406.

EXAMPLE 273

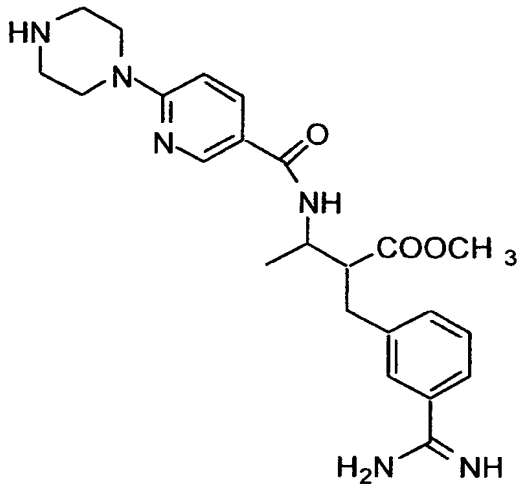
Compound 273



This material is prepared following the procedure described for compound 159a and substituting Compound 241. MS: $(M+H)^+$ 439.

EXAMPLE 274

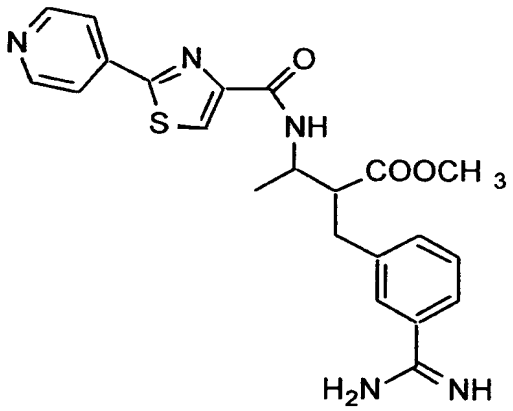
Compound 274



This material is prepared following the procedure described for compound 159a and substituting Compound 242. MS: $(M+H)^+$ 440.

EXAMPLE 275

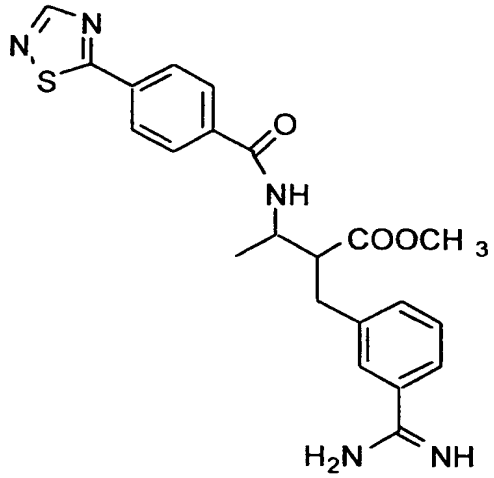
Compound 275



This material is prepared following the procedure described for compound 159a and substituting Compound 243. MS: $(M+H)^+$ 439.

EXAMPLE 276

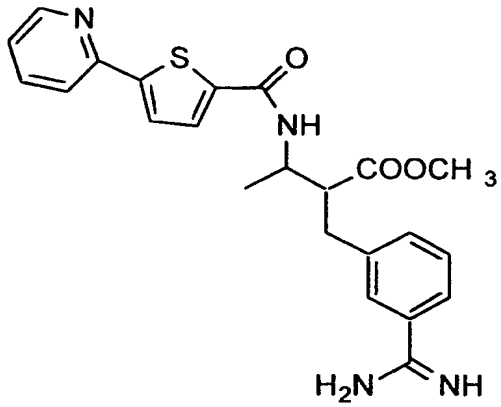
Compound 276



This material is prepared following the procedure described for compound 159a and substituting Compound 244. MS: $(M+H)^+$ 439.

EXAMPLE 277

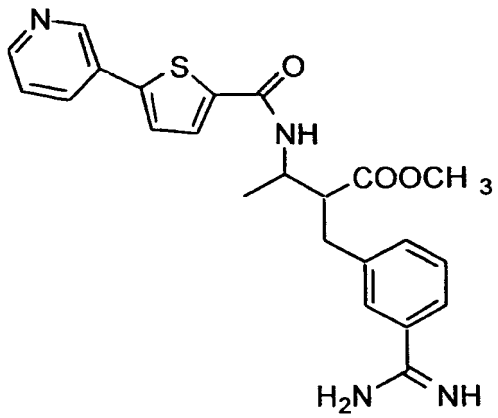
Compound 277



This material is prepared following the procedure described for compound 159a and substituting Compound 245. ^{1}H NMR (DMSO-d_6) δ 8.56-8.50 (m, 1H), 7.94-7.82 (m, 2H), 7.70 (s, 2H), 7.66-7.46 (m, 4H), 7.38-7.30 (m, 1H), 4.46-4.32 (m, 1H), 3.60 (s, 3H), 3.13-2.95 (m, 3H), 1.32 (d, J=7.2Hz, 3H). MS: $(M+H)^+$ 438.

EXAMPLE 278

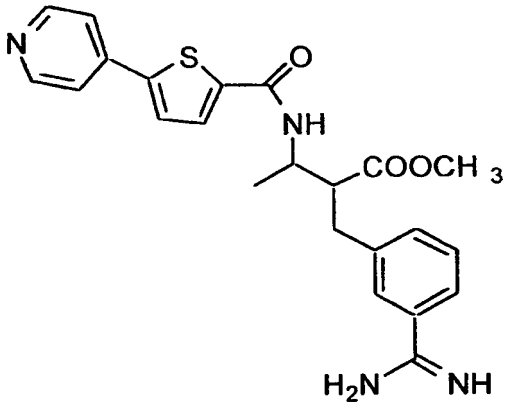
Compound 278



This material is prepared following the procedure described for compound 159a and substituting Compound 246. ^{1}H NMR (DMSO-d$_6$) δ 9.06 (s, 1H), 8.68-8.62 (m, 1H), 8.53 (d, J=8.4Hz, 1H), 7.85-7.78 (m, 1H), 7.75 (d, J=3.6Hz, 1H), 7.68 (d, J=3.6Hz, 1H), 7.65-7.45 (m, 4H), 4.48-4.33 (m, 1H), 3.57 (s, 3H), 3.13-3.00 (m, 3H), 1.32 (d, J=7.2Hz, 3H). MS: $(M+H)^+$ 438.

EXAMPLE 279

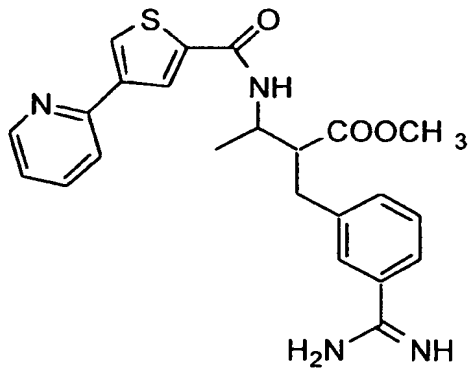
Compound 279



This material is prepared following the procedure described for compound 159a and substituting Compound 247. ^{1}H NMR (DMSO-d$_6$) δ 8.70 (s, 1H), 8.52 (d, J=9.6Hz, 1H), 8.18-8.08 (m, 1H), 7.96 (d, J=3.6Hz, 1H), 7.82 (d, J=3.6Hz, 1H), 7.65-7.45 (m, 4H), 4.50-4.35 (m, 1H), 3.57 (s, 3H), 3.13-3.02 (m, 3H), 1.34 (d, J=7.2Hz, 3H). MS: $(M+H)^+$ 438.

EXAMPLE 280

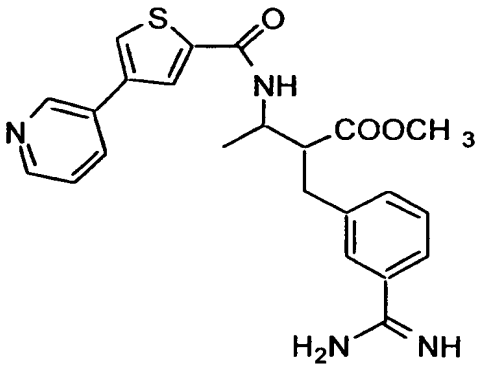
Compound 280



This material is prepared following the procedure described for compound 159a and substituting Compound 248. ^{1}H NMR (DMSO-d_6) δ 8.66 (d, J=6.0Hz, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.20-8.11 (m, 1H), 8.04 (d, J=7.2Hz, 1H), 7.65-7.44 (m, 5H), 4.50-4.35 (m, 1H), 3.60 (s, 3H), 3.17-3.02 (m, 3H), 1.33 (d, J=7.2Hz, 3H). MS: $(M+H)^+$ 438.

EXAMPLE 281

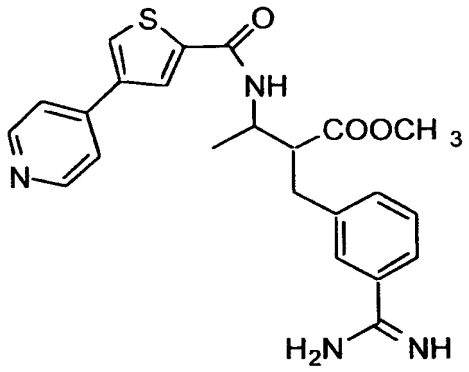
Compound 281



This material is prepared following the procedure described for compound 159a and substituting Compound 249. ^{1}H NMR (DMSO-d_6) δ 9.15-9.02 (m, 1H), 8.75-8.61 (m, 1H), 8.54 (d, J=8.4Hz, 1H), 8.22 (d, J=8.4Hz, 1H), 7.88-7.78 (m, 1H), 7.65-7.45 (m, 4H), 4.50-4.35 (m, 1H), 3.57 (s, 3H), 3.17-3.02 (m, 3H), 1.35 (d, J=7.2Hz, 3H). MS: $(M+H)^+$ 438.

EXAMPLE 282

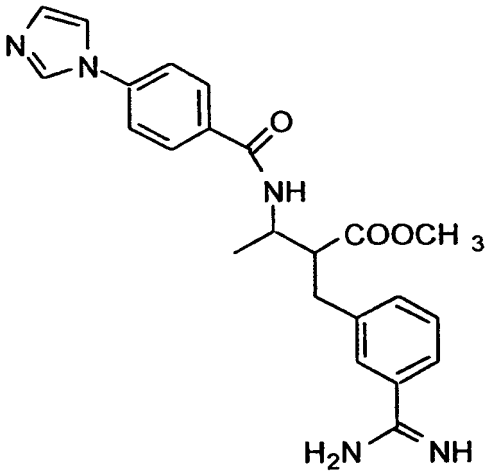
Compound 282



This material is prepared following the procedure described for compound 159a and substituting Compound 250. ^{1}H NMR (DMSO-d$_6$) δ 8.78 (s, 2H), 8.67 (s, 1H), 8.35 (s, 1H), 8.25 (d, J=8.4Hz, 2H), 7.65-7.45 (m, 4H), 4.50-4.38 (m, 1H), 3.57(s, 3H), 3.17-3.02 (m, 3H), 1.35 (d, J=7.2Hz, 3H). MS: $(M+H)^+$ 438.

EXAMPLE 283

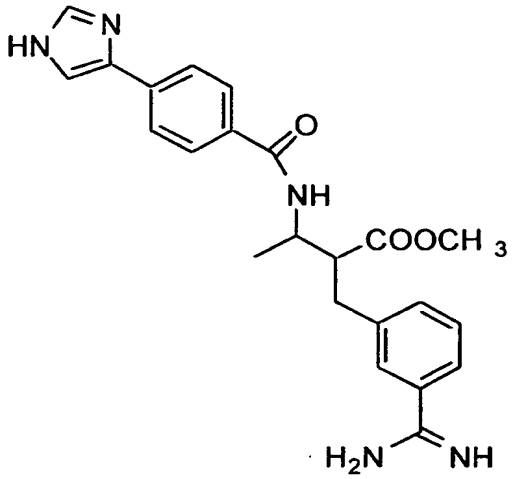
Compound 283



This material is prepared following the procedure described for compound 159a and substituting Compound 251. ^{1}H NMR (DMSO-d$_6$) δ 9.5 (s, 1H), 8.2 (s, 1H), 8.1 (d, J=5.0Hz, 2H), 7.9 (d, J=5.0Hz, 2H),, 7.8 (s, 1H), 7.5-7.7 (m, 4H), 4.4-4.6 (m, 1H), 3.6 (s, 3H), 3.0-3.2 (m, 3H), 1.4 (d, J=5.0Hz, 3H). MS: $(M+H)^+$ 421.

EXAMPLE 284

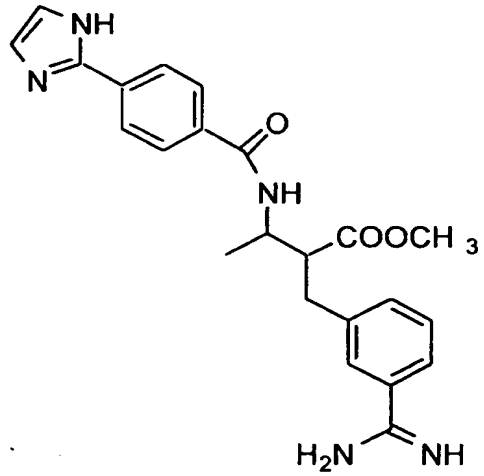
Compound 284



This material is prepared following the procedure described for compound 159a and substituting Compound 252. ^{1}H NMR (DMSO-d$_6$) δ 9.0 (s, 1H), 8.5 (d, J=5.0Hz, 1H), 8.1 (s, 1H), 8.0 (d, J=5.0Hz, 2H), 7.9 (d, J=5.0Hz, 2H), 7.5-7.7 (m, 4H), 4.4-4.6 (m, 1H), 3.6 (s, 3H), 3.0-3.2 (m, 3H), 1.4 (d, J=5.0Hz, 3H). MS: $(M+H)^+$ 421.

EXAMPLE 285

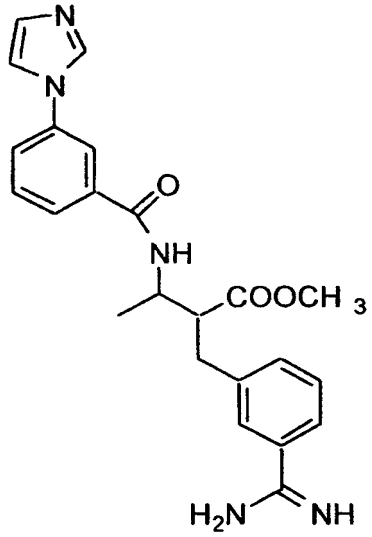
Compound 285



This material is prepared following the procedure described for compound 159a and substituting Compound 253. ^{1}H NMR (DMSO-d$_6$) δ 8.5 (d, J=5.0Hz, 1H), 7.80-8.10 (m, 4H), 7.8 (d, J=5.0Hz, 2H), 7.5-7.7 (m, 4H), 4.4-4.6 (m, 1H), 3.6 (s, 3H), 3.0-3.1 (m, 3H), 1.4 (d, J=5.0Hz, 3H). MS: $(M+H)^+$ 421.

EXAMPLE 286

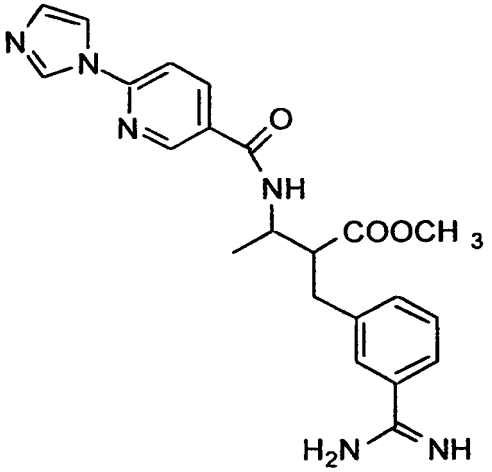
Compound 286



This material is prepared following the procedure described for compound 159a and substituting Compound 254. MS: $(M+H)^+$ 421.

EXAMPLE 287

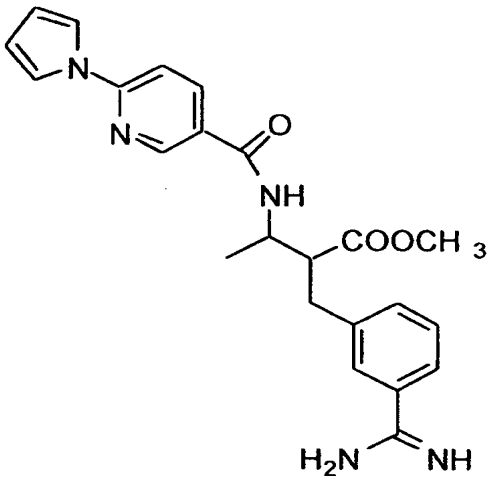
Compound 287



This material is prepared following the procedure described for compound 159a and substituting Compound 255. MS: $(M+H)^+$ 422.

EXAMPLE 288

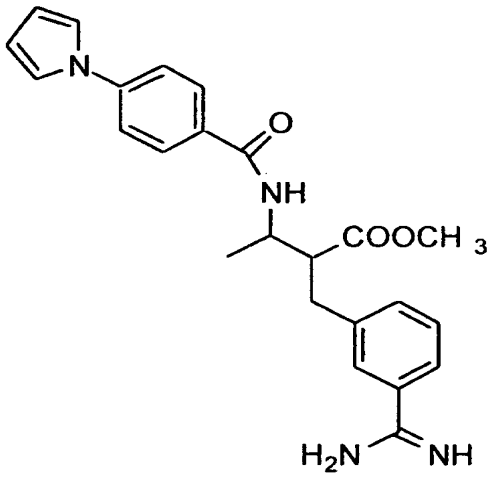
Compound 288



This material is prepared following the procedure described for compound 159a and substituting Compound 256. MS: $(M+H)^+$ 421.

EXAMPLE 289

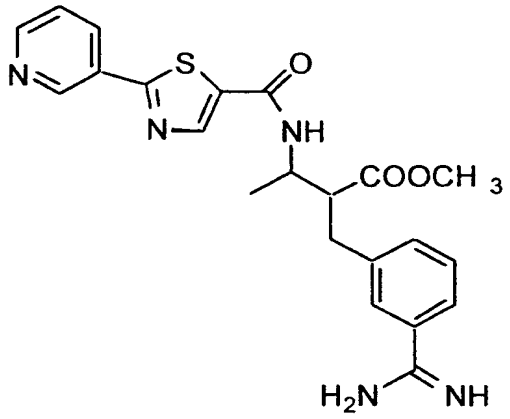
Compound 289



This material is prepared following the procedure described for compound 159a and substituting Compound 257. MS: $(M+H)^+$ 420.

EXAMPLE 290

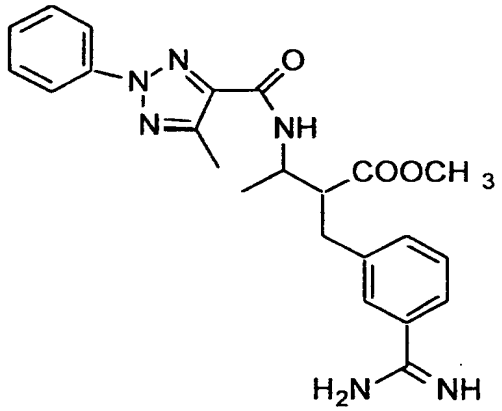
Compound 290



This material is prepared following the procedure described for compound 159a and substituting Compound 258. MS: $(M+H)^+$ 439.

EXAMPLE 291

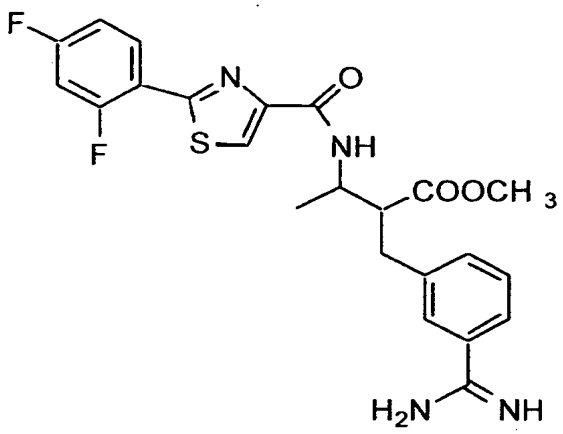
Compound 291



This material is prepared following the procedure described for compound 159a and substituting Compound 259. MS: $(M+H)^+$ 436.

EXAMPLE 292

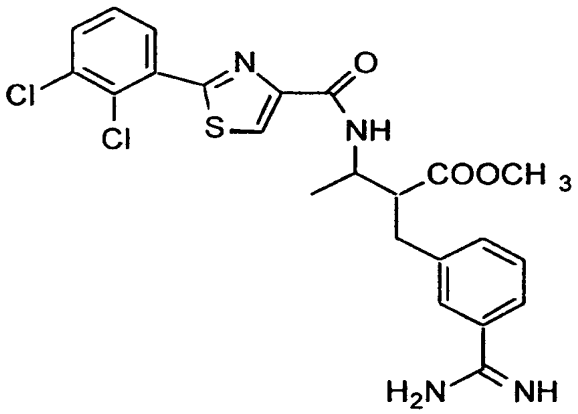
Compound 292



This material is prepared following the procedure described for compound 159a and substituting Compound 260. MS: $(M+H)^+$ 473.

EXAMPLE 293

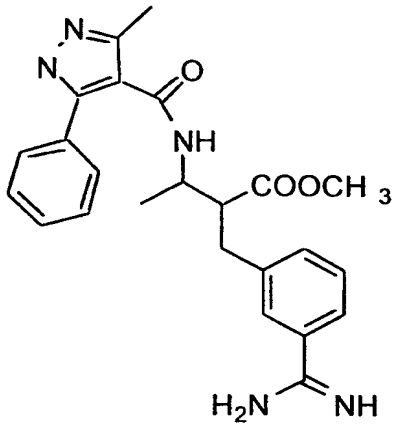
Compound 293



This material is prepared following the procedure described for compound 159a and substituting Compound 261. MS: $(M+H)^+$ 507.

EXAMPLE 294

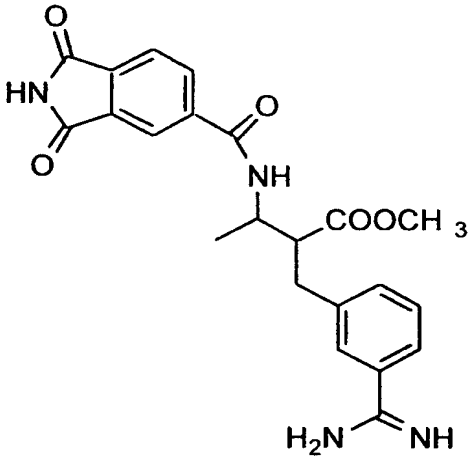
Compound 294



This material is prepared following the procedure described for compound 159a and substituting Compound 262. MS: $(M+H)^+$ 434.

EXAMPLE 295

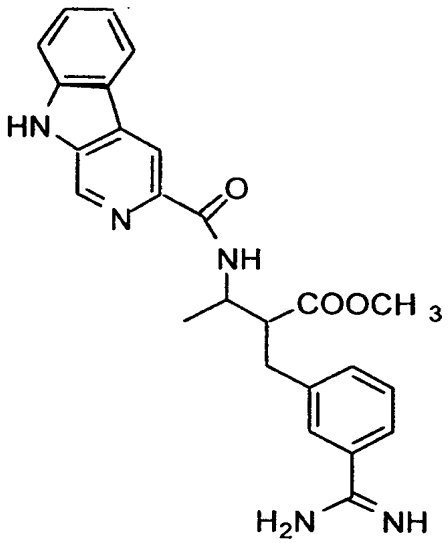
Compound 295



This material is prepared following the procedure described for compound 159a and substituting Compound 263. MS: $(M+H)^+$ 421.

EXAMPLE 296

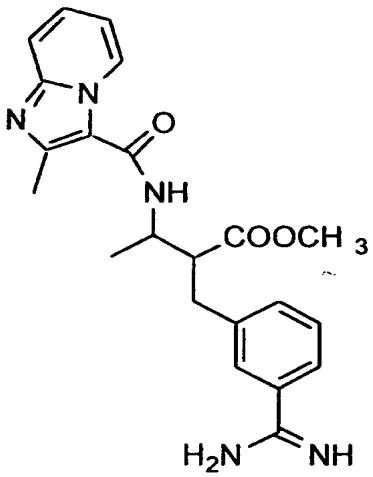
Compound 296



This material is prepared following the procedure described for compound 159a and substituting Compound 264. MS: $(M+H)^+$ 444.

EXAMPLE 297

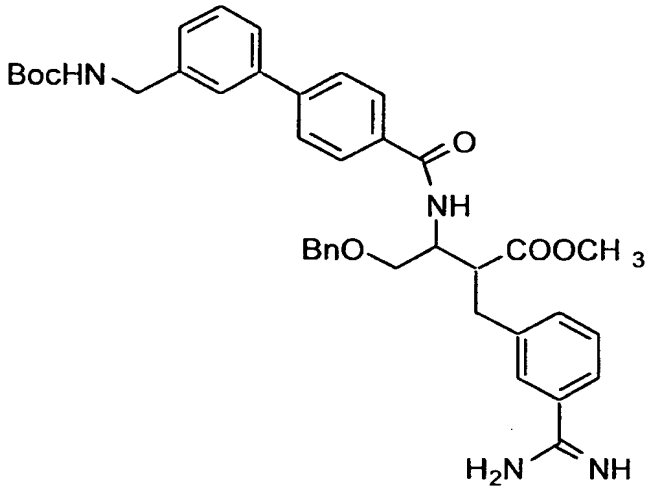
Compound 297



This material is prepared following the procedure described for compound 159a and substituting Compound 265. MS: $(M+H)^+$ 408.

EXAMPLE 298

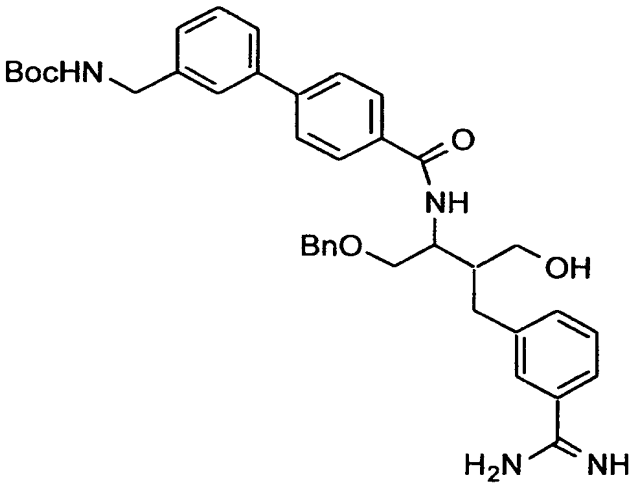
Compound 298



This material is prepared following the procedure described for compound 159b and substituting Compound 269.

EXAMPLE 299

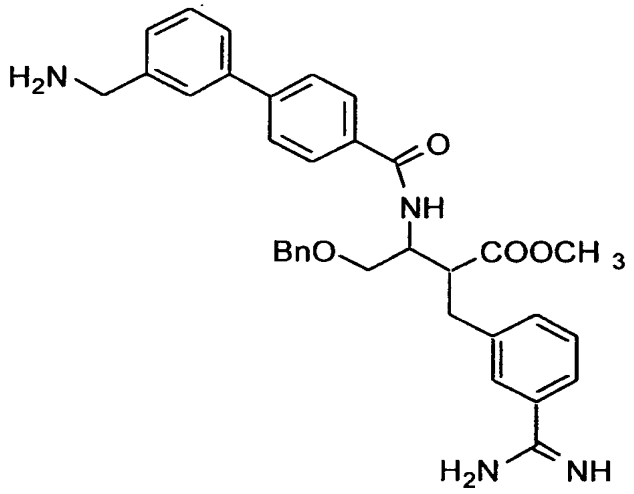
Compound 299



This material is prepared following the procedure described for compound 159b and substituting Compound 270.

EXAMPLE 300

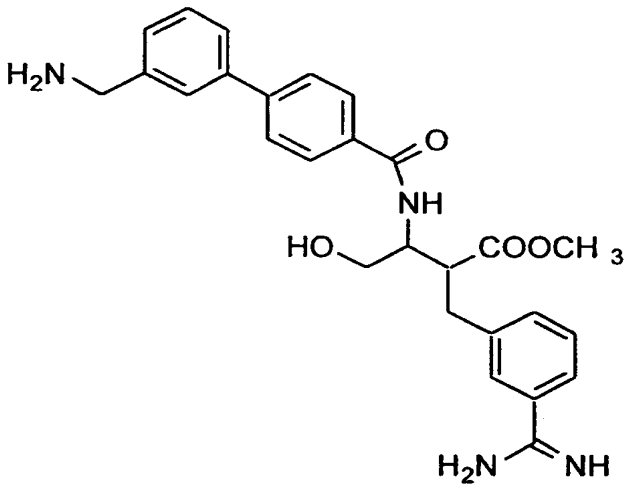
Compound 300



To a solution of compound 298 (1 mmol) in 20 mL of CH_2Cl_2 is added 5 mL of TFA at 0°C with stirring. Stirring is continued for 1 hour at 0°C and all solvents are removed in vacuo.

EXAMPLE 301

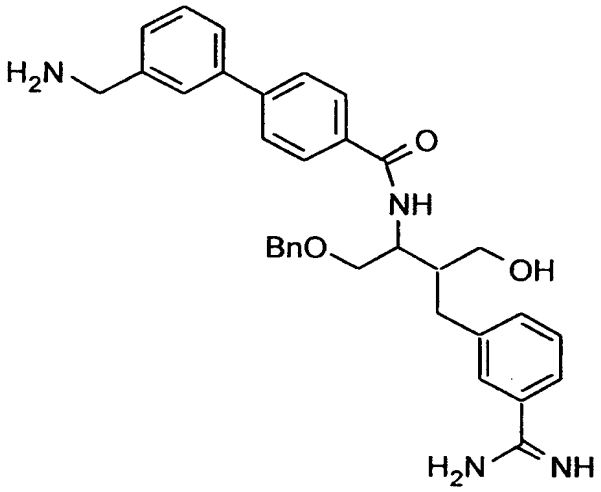
Compound 301



To a solution of compound 300 (1 mmol) in 25 mL of methanol is added approximately 50 mg of 10% palladium on charcoal. The mixture is shaken under a positive pressure of hydrogen (55 psi) for 24 hours and filtered. The filtrate is concentrated in vacuo and purified by reverse phase HPLC. ^{1}H NMR (DMSO-d_6) δ 8.3 (d, J=6.0Hz, 1H), 8.0 (d, J=5.0Hz, 2H), 7.8 (d, J=5.0Hz, 2H), 7.7 (d, J=6.0Hz, 2H), 7.4-7.7 (m, 6H), 4.3-4.5 (m, 1H), 4.2 (s, 2H), 3.8 (d, J=4.0Hz, 2H), 3.7 (s, 3H), 3.2-3.4 (m, 3H), 3.1-3.2 (m, 2H). MS: $(M+H)^+$ 475.

EXAMPLE 302

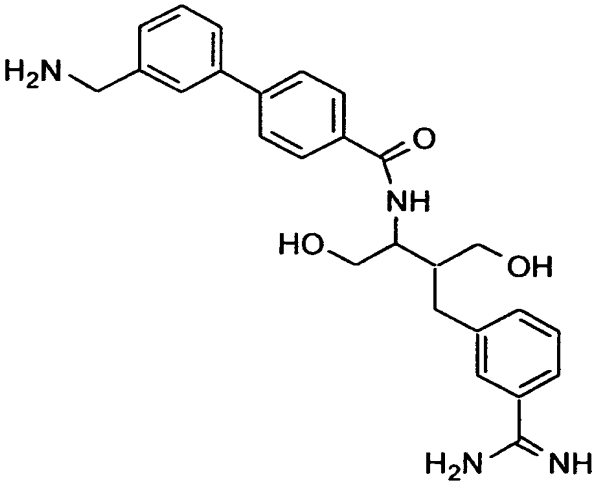
Compound 302



Compound 302 is prepared in a manner identical to compound 300, starting from compound 299.

EXAMPLE 303

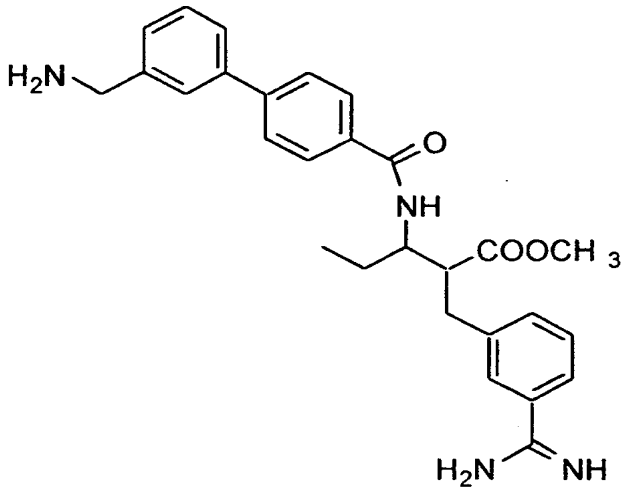
Compound 303



Compound 303 is prepared in a manner identical to compound 301, starting from compound 302. ^{1}H NMR (DMSO-d$_6$) δ 8.4 (d, J=5.0Hz, 1H), 8.0 (d, J=5.0Hz, 2H), 7.8 (d, J=5.0Hz, 2H), 7.7 (d, J=4.0Hz, 2H), 7.5-7.7 (m, 6H), 4.2 (s, 2H), 4.1-4.2 (m, 1H), 4.0 (dd, J=8.0, 2.0Hz, 1H), 3.8 (s, 2H), 3.7 (dd, J=8.0, 2.0Hz, 1H), 3.0 (d, J=5.0Hz, 2H), 2.2-2.4 (m, H). MS: $(M+H)^+$ 448.

EXAMPLE 304

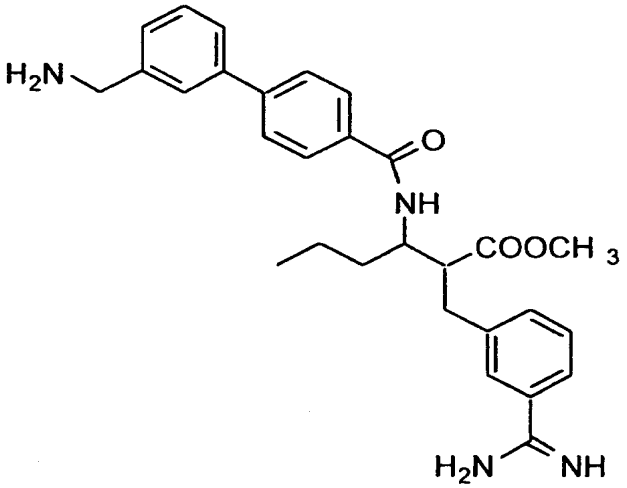
Compound 304



Compound 304 is prepared by procedures substantially similar to those used to prepare compound 301, starting from the appropriate materials. ^{1}H NMR (CD_3OD) δ 7.94 (d, J=10.8Hz, 2H), 7.85-7.72 (m, 4H), 7.70-7.45 (m, 6H), 4.32-4.23 (m, 1H), 4.22 (s, 2H), 3.62 (s, 3H), 3.83-3.55 (m, 2H), 3.18-3.02 (m, 3H), 0.94 (t, J=8.4Hz, 3H). MS: $(M+H)^+$ 474.

EXAMPLE 305

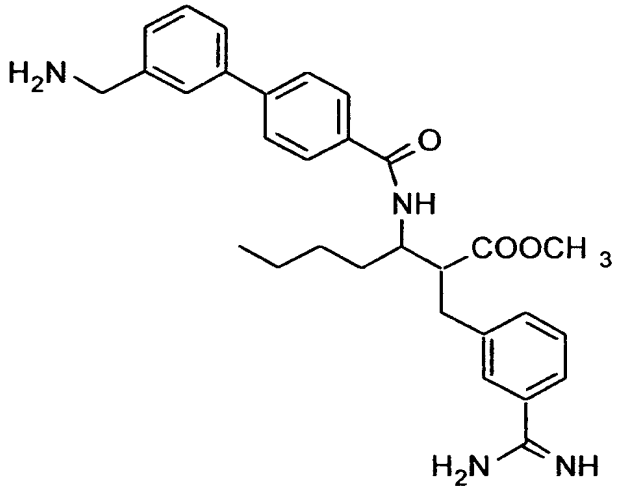
Compound 305



Compound 305 is prepared by procedures substantially similar to those used to prepare compound 301, starting from the appropriate materials. ^{1}H NMR (CD_3OD) δ 7.94 (d, J=10.8Hz, 2H), 7.85-7.72 (m, 4H), 7.68-7.45 (m, 6H), 4.42-4.30 (m, 1H), 4.22 (s, 2H), 3.61 (s, 3H), 3.15-3.02 (m, 3H), 1.72-1.58 (m, 2H), 1.51-1.32 (m, 2H), 0.93 (t, J=8.4Hz, 3H). MS: $(M+H)^+$ 488.

EXAMPLE 306

Compound 306



Compound 306 is prepared by procedures substantially similar to those used to prepare compound 301, starting from the appropriate materials. ^{1}H NMR (CD_3OD) δ 7.93 (d, J=10.8Hz, 2H), 7.85-7.72 (m, 4H), 7.70-7.45 (m, 6H), 4.42-4.30 (m, 1H), 4.22 (s, 2H), 3.62 (s, 3H), 3.14-3.02 (m, 3H), 1.78-1.60 (m, 2H), 1.45-1.25 (m, 4H), 0.90 (t, J=8.4Hz, 3H). MS: $(M+H)^+$ 502.

EXAMPLE 307

Compound 307

(Z)-N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)allyl]-4-pyridin-3-ylbenzamide.

A. 5-Iodo-2-(2-methoxyethoxymethoxy)benzaldehyde.

A 1 M solution of Iodine monochloride in dichloromethane (410 mL, 0.41 mol) is added to a solution of salicylaldehyde (50 g, 0.41 mol) in dichloromethane (150 mL) at 0 °C. The resulting solution is warmed to room temperature and stirred overnight. The deep colored solution is discharged with saturated aqueous Na_2SO_3 (100 mL). The organic layer is separated, washed with water, dried over $MgSO_4$, filtered and concentrated. The crude product is recrystallized from cyclohexane to give 4-iodosalicylaldehyde as yellow crystals (61 g, 0.25 mol). A solution of 4-iodosalicylaldehyde (12.4 g, 50 mmol) and MEM chloride (6 mL, 53 mmol) in THF (50 mL) is added to a suspension of 60% NaH (2.2 g, 55 mmol) in THF (50 mL) at 0 °C. The resulting mixture is stirred at room temperature for 2 hours. Aqueous workup and concentration gives product as a liquid (15 g, 45 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.36 (s, 1H), 8.11 (d, 1H), 7.73 (dd, 1H), 7.03 (d, 1H), 5.37 (s, 2H), 3.88 (t, 2H), 3.52 (t, 2H), 3.36 (s, 3H). EI MS $[M]^+$ = 436.

B. (Z, E)-3-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propenyl]-4-(2-methoxy-ethoxymethoxy)benzonitrile.

Potassium t-butoxide (1.85 g, 16,5 mmol) is added to a suspension of 5-iodo-2-(2-methoxy-ethoxymethoxy)benzaldehyde (5 g, 15 mmol) and [2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)ethyl]-triphenyl-phosphonium bromide (7.7 g, 15 mmol) in THF (80 mL). The mixture is stirred at room temperature overnight. the precipitated solid is removed, the filtrate is concentrated, diluted with water and extracted twice with $CHCl_3$. The combined organic layers are washed with water, dried over $MgSO_4$, filtered and concentrated. The crude product is purified by chromatography (10% to 30% EtOAc/hexanes) to give a yellow solid (3.1 g, 6.3 mmol). This product (2.5 g, 5.1 mmol) is mixed with $ZnCN_2$ (2.1 g, 17.5 mmol) and $(Ph_3P)_4Pd$ (0.3 g, 0.26 mmol) in DMF (15 mL). The mixture is heated at 75 °C for 4 hours, then cooled, diluted with EtOAc, washed with 5% NH_4OH, water and brine (5x25 mL), dried over $MgSO_4$, filtered and concentrated. The crude product is purified by flash chromatography (15% to 30% EtOAc/hexanes) to give a mixture of two isomers (Z/E = 4/1) as a white solid (1.0 g, 26 mmol). Fab MS $[M+1]^+ = 393$.

C. (Z)-3-(3-Aminopropenyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile.

(Z, E)-3-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)propenyl]-4-(2-methoxyethoxy-methoxy)benzonitrile (0.2 g, 0.51 mmol) and NH_2NH_2 hydrate (0.15 mL, 3 mmol) in 1-butanol (10 mL) is heated to 90 °C for 1 hour. The reaction is cooled and the resulting suspension is filtered. The filtrate is concentrated to a residue which is purified by chromatography (15% to 20% EtOH/ CH_2Cl_2). The high Rf material is identified as the Z-isomer (30 mg, 0.11 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (dd, 1H), 7.45 (d, 1H), 7.20 (d, 1H), 6.50 (d, 1H), 5.9 (m, 1H), 5.37 (s, 2H), 3.80 (t, 2H), 3.50 (m, 4H), 3.30 (s, 3H). EI MS $[M]^+ = 262$.

D. (Z)-N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-allyl]-4-pyridin-3-yl-benzamide.

(Z)-3-(3-Aminopropenyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile (30 mg, 0.11 mmol) in DMF (2 mL) is added to the mixture of 4-pyridin-3-yl benzoic acid (24 mg, 0.12 mmol), TBTU (39 mg, 0.12 mmol), and Et_3N (12 mg, 0.12 mmol) in DMF (0.5 mL), and stirred at room temperature overnight. The solution is diluted with water and extracted with CH_2Cl_2 (3X). The combined CH_2Cl_2 layers are washed with water, dried over $MgSO_4$, filtered and concentrated. The crude product is purified by chromatography in a gradient of 2% MeOH/CH_2Cl_2 to give a white solid (35 mg, 0.079 mmol). The above product is treated with HCl gas in EtOH (9 mL) for 20 min, then sealed and stirred overnight. After concentrating to dryness, the product is treated with a saturated solution of NH_3 gas in MeOH (10 mL) at 50 °C for 2 hours. The reaction is sealed and stirred at room temperature overnight. White solid is

collected and washed with MeOH. More product is obtained from the filtrate after concentrating to a small volume (26 mg combined, 0.07 mmol). ^{1}H NMR (DMSO, 300 MHz) δ 9.05 (bs, 1H), 8.95 (s, 1H), 8.60 (s, 1H), 8.15 (d, 1H), 7.97 (d, 2H), 7.84 (d, 2H), 7.50 (m, 2H), 7.40 (d, 1H), 6.57 (d, 1H), 6.20 (d, 1H), 5.50 (m, 1H), 4.17 (bs, 2H). Ion spray MS [M+1]+ = 373, $[M+2]^{2+}$ = 187.

EXAMPLE 308

Compound 308

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-pyridin-3-yl)-benzamide ditrifluoroacetate.

(Z)-N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-allyl]-4-pyridin-3-yl-benzamide (22 mg, 0.059 mmol) is dissolved in MeOH (10 mL) and hydrogenated at 30 psi H_2 for 2 hours in the present of 5% Pd/C. The mixture is filtered, washed with MeOH, and concentrated. The product is purified by HPLC eluting with a gradient of 10% MeCN/H_2O (0.1% TFA) to 100% MeCN. Lyophylization of the appropriate fraction gives the title compound as a white solid (35 mg, 0.056 mmol). ^{1}H NMR (DMSO, 300 MHz) δ 10.6 (bs, 1H), 8.97 (bs, 2H), 8.70 (m, 3H), 8.20 (d, 1H), 7.90 (d, 2H), 7.80 (d, 2H), 7.55 (m, 3H), 6.90 (d, 1H), 3.25 (t, 2H), 2.60 (t, 2H), 1.78 (m, 2H). Ion spray MS [M+1]+ = 375, $[M+2]^{2+}$ = 188.

EXAMPLE 309

Compound 309

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(1-oxy-pyridin-4-yl)-benzamide ditrifluoroacetate.

A. 3-(3-Aminopropyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile.

(Z, E)-3-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)propenyl]-4-(2-methoxy-ethoxymethoxy)benzonitrile (0.38 g, 0.97 mmol) in 50% MeOH/CH_2Cl_2 (10 mL) is hydrogenated (H_2 filled balloon) overnight in the presence of 5% Pd/C. The mixture is filtered, washed with CH_2Cl_2, and concentrated. The above residue and NH_2NH_2 hydrate (0.23 mL, 4.6 mmol) in 1-butanol (15 mL) is heated to 90 °C for 1 hour. After cooling, the solid is removed by filtration, and washed with 1-butanol. The filtrate is concentrated to give the title compound as a light yellow solid (0.23 g, 0.87 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (m, 2H), 7.17 (d, 1H), 5.34 (s, 2H), 3.82 (t, 2H), 3.55 (t, 2H), 3.38 (s, 3H), 2.70 (m, 4H), 1.70 (m, 2H).

B. N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(1-oxy-pyridin-4-yl)-benzamide ditrifluoroacetate.

3-(3-Aminopropyl)-4-(2-methoxyethoxymethoxy)benzonitrile (88 mg, 0.33 mmol) in DMF (0.5 mL) is added to a mixture of 4-pyridin-4-yl benzoic acid (60 mg, 0.3 mmol), TBTU (106 mg, 0.33 mmol), and Et_3N (0.043 mL, 0.033 mmol) in DMF (1 mL). The mixture is stirred at 35 °C for 4 hours.

The solution is diluted with EtOAc (20 mL), washed with saturated $NaHCO_3$ (3X17 mL) and brine (3X17 mL), dried over $MgSO_4$, filtered and concentrated. The residue is chromatographed (4% $MeOH/CH_2Cl_2$) to give 3-[4-(pyridin-4-yl)-benzamido]propyl)-4-(2-methoxyethoxymethoxy)-benzonitrile (0.09 g, 0.20 mmol), contaminated with an unknown byproduct. The crude material (0.08 g, 0.18 mmol) is dissolved in CH_2Cl_2 (5 mL), treated with MCPBA (57-86%, 92 mg) at 0 °C, and stirred at room temperature for 2 hours. The residue from aqueous workup and concentration is treated with anhydrous HCl/EtOH followed by ammonolysis as described in Example 307, part D. HPLC purification (10% MeCN/0.1% TFA in H_2O to 100% MeCN) gave the title compound (0.007 g, 0.01 mmol). ^1H NMR (CD_3OD, 300 MHz) δ 8.94 (bs, 1H), 8.65 (bs, 1H), 8.40 (m, 3H), 7.90 (m, 6H), 7.64 (d, 1H), 7.57 (dd, 1H), 6.93 (d, 1H), 3.43 (t, 2H), 2.77 (t, 2H), 1.97 (m, 2H). Ion spray MS $[M+1]+ = 391$, $[M+2]^{2+} = 196$.

EXAMPLE 310

Compound 310

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(6-oxo-1,6-dihydropyridin-3-yl-benzamide trifluroacetate.

A. 3-[4-(6-oxo-1,6-dihydropyridin-3-yl)-benzamido]propyl)-4-hydroxybenzonitrile.

3-(3-Aminopropyl)-4-(2-methoxyethoxymethyl)benzonitrile (0.048 g, 0.18 mmol) is treated with 4-(6-methoxypyridin-3-yl)benzoic acid (0.042 g, 0.18 mmol), TBTU (0.058, 0.18 mmol), and triethylamine (0.025 mL), as described in EXAMPLE 309, part B to give, after chromatography (CH_2Cl_2 to 5% $MeOH/CH_2Cl_2$), 3-[4-(6-methoxypyridin-3-yl)-benzamido]propyl)-4-(2-methoxyethoxymethoxy)-benzonitrile. This material is heated with pyridinium hydrochloride to a melt for 15 minutes. The reaction mixture is cooled and diluted with water (20 mL); the precipitated product, 3-{3-[4-(6-methoxypyridin-3-yl)-benzamido]propyl}-4-hydroxybenzonitrile is collected by filtration (0.031 g, 0.083 mmol). ^1H NMR (CD_3OD, 300 MHz) δ 8.1 (m, 1H), 7.97 (m, 1H), 7.90 (AB, 2H), 7.76 (bs, 1H), 7.60 (AB, 2H), 7.95 (s, 1H), 7.40 (d, 1H), 6.93 (d, 1H), 6.87 (d, 1H), 6.67 (d, 1H), 3.45 (t, 2H), 2.73 (t, 2H), 1.93 (m, 2H). Ion spray MS $[M+1]^+ = 374$.

B. N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(6-oxo-1,6-dihydropyridin-3-yl-benzamide trifluroacetate.

3-{3-[4-(6-methoxypyridin-3-yl)-benzamido]propyl}-4-hydroxybenzonitrile is converted to the title compound by anhydrous HCl/EtOH followed by ammonolysis as described in Example 307, part D. HPLC purification (10% MeCN/0.1% TFA in H_2O to 100% MeCN) yielded the title compound (0.018 g,

0.046 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.94 (bs, 1H), 8.53 (bs, 1H), 8.0 (dd, 1H), 7.92 (AB, 2H), 7.84 (s, 1H), 7.65 (m, 3H), 7.56 (dd, 1H), 6.95 (d, 1H), 6.67(d, 1H), 3.42 (t, 2H), 2.77 (t, 2H), 1.98 (m, 2H). Ion spray MS $[M+1]^+ = 391$.

EXAMPLE 311

Compound 311

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(pyridazin-4-yl)benzamide ditrifluoroacetate.

A. 3-{3-[4-(Pyridazin-4-yl)benzamido]propyl}-4-(2-methoxyethoxymethoxy)-benzonitrile.

3-(3-Aminopropyl)-4-(2-methoxyethoxymethyl)benzonitrile (0.05 g, 0.19 mmol) is treated with 4-(pyridazin-4-yl)benzoic acid (0.038 g, 0.18 mmol), TBTU (0.058 g, 0.18 mmol), and triethylamine (0.035 mL), as described in EXAMPLE 309, part B to give, after chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2), the title compound. (0.045 g, 0.10 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.47 (d, 1H), 9.27 (d, 1H), 7.97 (AB, 2H), 7.63 (AB, 2H), 7.69 (dd, 1H), 7.46 (s, 1H), 7.18 (d, 1H), 6.69 (d, 1H), 5.37 (s, 2H), 3.82 (m, 2H), 3.50 (m, 4H), 3.35 (s, 3H), 2.73 (t, 2H), 1.97 (m, 2H). Ion Spray MS, $[M+H]^+ =$ 447.

B. N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(pyridazin-4-yl)benzamide ditrifluroacetate.

3-{3-[4-(Pyridazin-4-yl)benzamido]propyl}-4-(2-methoxyethoxymethoxy)-benzonitrile (0.045 g, 0.10 mmol) is converted to the title compound by anhydrous HCl/EtOH treatment followed by ammonolysis as described in EXAMPLE 307, part D. HPLC purification gave the title compound (0.025 g, 0.066 mmol). ^{1}H NMR (DMSO, 300 MHz) δ 10.65 (s, 1H), 9.70 (s, 1H), 9.30 (d, 1H), 9.0 (bs, 2H), 8.71 (m, 3H), 8.05 (m, 5H), 7.63 (s, 1H), 7.55 (dd, 1H), 6.95 (d, 1H), 3.3 (m, 2H), 2.64 (t, 2H), 1.85 (m, 2H). Ion spray MS $[M+1]^+ = 376$.

EXAMPLE 312

Compound 312

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-7-chlorobenzothiophene-2-carboxamide trifluroacetate.

3-(3-Aminopropyl)-4-(2-methoxyethoxymethyl)benzonitrile (0.05 g, 0.19 mmol) is treated with 7-chlorobenzothiophene-2-carboxylic acid (0.044 g, 0.020 mmol), TBTU (0.058, 0.18 mmol), and triethylamine (0.025 mL), as described in EXAMPLE 309, part B to give, after chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2), 3-{3-[7-chlorobenzo-thiophene-2-carboxamido]propyl}-4-(2-methoxyethoxymethoxy)-benzonitrile. (0.020 g, 0.048 mmol); Ion Spray MS, $[M+H]^+ = 447$. This material is treated with anhydrous HCl/EtOH followed by ammonolysis as described in EXAMPLE 307,

part D. HPLC purification (10% MeCN/0.1% TFA in H_2O to 100% MeCN) gave the title compound (0.005 g, 0.012 mmol). ^1H NMR (DMSO, 300 MHz) δ 10.66 (s, 1H), 9.01 (s, 2H), 8.78 (m, 1H), 8.64 (bs, 2H), 8.22 (s, 1H), 8.08 (s, 1H), 7.88 (d, 1H), 7.66 (d, 1H), 7.56 (dd, 1H), 7.47 (dd, 21H), 6.95 (d, 1H), 3.32 (m, 2H), 2.65 (t, 2H), 1.86 (m, 2H). Ion spray MS $[M+1]^+ = 388,390$.

EXAMPLE 313

Compound 313

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate.

A. (E)-3-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propenyl]-4-(2-methoxy-ethoxymethoxy) benzonitrile.

A solution of 2-bromo-4-cyanophenol (5 g, 25 mmol) and MEM chloride (3 mL, 26 mmol) in THF (25 mL) is added to a suspension of NaH (60%, 1.1 g, 28 mmol) in THF (25 mL) at 0 °C. The resulting mixture is stirred at room temperature for 2 h, concentrated, diluted with EtOAc, washed with 1 N NaOH and water. The organic layer is dried over $MgSO_4$ and concentrated to obtain a clear liquid (6.6 g, 23 mmol). The product (5.6 g, 20 mmol) is treated with N-allylphthalimide (4 g, 21 mmol), $Pd(OAc)_2$ (0.13 g, 0.58 mmol), $P(o\text{-}tol)_3$ (0.37 g, 1.2 mmol), and Et_3N (5.6 mL, 40 mmol). The reaction mixture is heated at 100 °C in sealed tube overnight, cooled, diluted with EtOAc and washed with water (3x100 mL). The organic layer is dried ($MgSO_4$) and concentrated. The residue is chromatographed (20% to 50% EtOAc/hexanes) to give the title compound as a white solid (3.5 g, 8.9 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (m, 2H), 7.72 (m, 2H), 7.65 (d, 1H), 7.44 (d, 1H), 7.18 (d, 1H), 6.90 (d, 1H), 6.30 (m, 1H), 5.33 (s, 2H), 4.46 (d, 2H), 3.80 (d, 2H), 3.52 (d, 2H), 3.40 (s, 3H).

B. (E)-3-(3-Aminopropenyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile.

(E)-3-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)propenyl]-4-(2-methoxy-ethoxymethoxy)-benzonitrile (3.1 g, 8.0 mmol) and NH_2NH_2 hydrate (0.96 mL, 20 mmol) in ethanol (100 mL) is refluxed for 1.5 hours. The mixture is concentrated, treated with aqueous NaOH, and extracted with CH_2Cl_2 (3X). The CH_2Cl_2 layer is dried and concentrated to obtain the product as a clear oil (1.9 g, 7.2 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, 1H), 7.47 (dd, 1H), 7.22 (d, 1H), 6.75 (d, 1H), 6.34 (m, 1H), 5.35 (s, 2H), 3.80 (t, 2H), 3.50 (m, 4H), 3.27 (s, 3H).

C. (E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate.

A solution of (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile (0.12 g, 0.46 mmol) in DMF is treated with 6-methoxy-pyridin-3-yl)-benzoic acid, TBTU and Et_3N as described in EXAMPLE 309, part B. Standard workup and chromatography gives the desired 3-{3-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)benzamido]propyl}-4-(2-methoxyethoxy-methoxy)-benzonitrile (0.22 g, 0.46 mmol). A portion of the benzonitrile (0.09 g, 0.19 mmol) is converted to the benzamidine by treatment with anhydrous HCl/EtOH followed by ammonolysis as described in EXAMPLE 307, part D. The product is purified by HPLC eluting with a gradient of 10% MeCN/H_2O (0.1% TFA) to 100% MeCN to give title compound as a white solid (0.05 g, 0.12 mmol). ^1H NMR (CD_3OD, 300 MHz) δ 8.43 (d, 1H), 7.95 (m, 4H), 7.70 (d, 2H), 7.55 (dd, 1H), 6.90 (m, 3H), 6.53 (m, 1H), 4.18 (d, 2H), 3.95 (s, 3H). Ion spray MS $[M+1]^+ = 403$.

EXAMPLE 314

Compound 314

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide trifluoroacetate.

(E)-3-{3-[4-(6-methoxypyridin-3-yl)benzamido]propenyl}-4-(2-methoxyethoxymethoxy)-benzonitrile (0.12 g, 0.25 mmol), prepared as described in EXAMPLE 313, Part C, is treated with pyridinium hydrochloride as described in EXAMPLE 310, Part A to obtain a white solid (0.087 g, 0.24 mmol). This material is treated with anhydrous HCl/EtOH followed by ammonolysis as described in EXAMPLE 307, part D. The crude product is purified by HPLC eluting with a gradient of 10% MeCN/H_2O (0.1% TFA) to 100% MeCN, followed by recrystallization (CH3CN/MeOH) to give title compound as a white solid (0.03 g, 0.077 mmol). ^1H NMR (DMSO, 300 MHz) δ 11.92 (bs, 1H), 10.85 (s, 1H), 9.03 (s, 2H), 8.82 (t, 1H), 8.65 (s, 2H), 7.85 (m, 5H), 7,65 (d, 2H), 7.55 (d, 1H), 6.94 (d, 1H), 6,72 (d, 1H), 6.42 (m, 2H), 4.08 (t, 2H). Ion spray MS $[M+1]^- = 389$.

EXAMPLE 315

Compound 315

(E)-Biphenyl-4-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide trifluoroacetate.

A solution of (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile (0.04 g, 0.2 mmol) in DMF (0.5 mL) is treated with Biphenyl-4-carboxylic acid (0.042 g, 0.21 mmol), TBTU (0.07 g, 0.22 mmol) and Et_3N (60 mL, 0.44 mmol) for 4 hours at 35 °C, then overnight at room temperature. The reaction mixture is diluted with ethyl acetate (8 mL), washed with water (3 X 2 mL) and concentrated to a residue under a stream of nitrogen. The residue is treated with absolute ethanol (5 mL) cooled and saturated with HCl gas; the reaction container is sealed and the solution is stirred overnight at room tempera-ture. The solvent and excess HCl are removed by a stream of nitrogen; the residue is

dissolved in MeOH (5 mL), cooled and saturated with NH_3 gas. The reaction container is sealed and the solution is stirred overnight at room temperature. The solvent and excess NH_3 are removed by a stream of nitrogen. The residue is subjected to HPLC purification eluting with a gradient of 10% MeCN/H_2O (0.1% TFA) to 100% MeCN. Lyophylization of the appropriate fraction gives the title compound as a white solid (0.012 g, 0.032 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.84 (t, 1H), 7.92 (m, 3H), 7.70 (d, 2H), 7.65 (d, 2H), 7.54 (dd, 1H), 7.42 (m, 3H), 6.92 (m, 2H), 6.50 (m, 1H), 4.20 (t, 2H). Ion spray MS $[M+1]^+ = 372$.

In a like manner, by the method described in EXAMPLE 315, the compounds of EXAMPLES 316-324 are prepared:

EXAMPLE 316

Compound 316

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-pyridin-3-yl-benzamide ditrifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile and 4-pyridin-3-yl-benzoic acid. ^{1}H NMR (DMSO, 300 MHz) δ 10.87 (s, 1H), 9.05 (s, 2H), 9.00 (s, 1H), 8.90 (t, 1H), 8.73 (s, 2H), 8.61 (d, 1H), 8.25 (d, 1H), 8.00 (d, 2H), 7.85 (m, 3H), 7,57 (m, 2H), 6.95 (d, 1H), 6.70 (d, 1H), 6.45 (m, 1H), 4.08 (t, 2H). Ion spray MS [M+1]+ = 373, $[M+2]^{2+} = 187$.

EXAMPLE 317

Compound 317

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-pyridin-4-yl-benzamide ditrifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy)benzonitrile and 4-pyridin-4-yl-benzoic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.97 (t, 1H), 8.80 (d, 2H), 8.22 (d, 2H), 8.00 (m, 5H), 7.55 (dd, 1H), 6.90 (m, 2H), 6.55 (m, 1H), 4.22 (t, 2H). Ion spray MS $[M+1]^+ = 373$, $[M+2]^{2+} = 187$.

EXAMPLE 318

Compound 318

(E)-Biphenyl-3,4'-dicarboxylic acid 3-amide 4'-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide} trifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and biphenyl-3,4'-dicarboxylic acid 3-amide. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.87 (t, 1H),

8.18 (s, 1H), 7.96 (d, 2H), 7.85 (m, 5H), 7.55 (m, 2H), 6.95 (m, 2H), 6.53 (m, 1H), 4.21 (t, 2H). Ion spray MS $[M+1]^+ = 415$.

EXAMPLE 319

Compound 319

(E)-4-tert-Butyl-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-benzamide trifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and 4-*tert*-butylbenzoic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.72 (t, 1H), 7.90 (d, 1H), 7.78 (d, 2H), 7.50 (m, 3H), 6.90 (m, 2H), 6.50 (m, 1H), 4.17 (t, 2H), 1.34 (s, 9H). Ion spray MS $[M+1]^+ = 352$.

EXAMPLE 320

Compound 320

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(3H-imidazol-4-yl)-benzamide ditrifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and 4-(3H-imidazol-4-yl)benzoic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.90 (m, 2H), 8.00 (m, 3H), 7.90 (d, 1H), 7.85 (d, 2H), 7.57 (dd, 1H), 6.93 (m, 2H), 6.53 (m, 1H), 4.20 (t, 2H). Ion spray MS $[M+1]^+ = 362$, $[M+2]^{2+} = 181.4$.

EXAMPLE 321

Compound 321

(E)-Biphenyl-4,4'-dicarboxylic acid 4'-amide 4-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide} trifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and biphenyl-4,4'-dicarboxylic acid 4'-amide. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.87 (t, 1H), 7.96 (m, 5H), 7.79 (m, 4H), 7.55 (d, 1H), 6.90 (m, 2H), 6.50 (m, 1H), 4.22 (t, 2H). Ion spray MS $[M+1]^+ = 415$.

EXAMPLE 322

Compound 322

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(1H-imidazol-2-yl)-benzamide ditrifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and 4-(1H-imidazol-2-yl)-benzoic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.02 (t, 1H), 8.08

(d, 2H), 8.00 (d, 2H), 7.90 (d, 1H), 7.67 (s, 2H), 7.53 (dd, 1H), 6.90 (m, 2H), 6.53 (m, 1H), 4.19 (t, 2H). Ion spray MS $[M+1]^+ = 362$, $[M+2]^{2+} = 181.6$.

EXAMPLE 323

Compound 323

(E)-3-Oxo-2,3-dihydro-thieno[3,2-c]pyridazine-6-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide trifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and 3-oxo-2,3-dihydro-thieno[3,2-c]pyridazine-6-carboxylic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.90 (d, 1H), 7.74 (s, 1H), 7.55 (dd, 1H), 7.40 (s, 1H), 6.90 (m, 2H), 6.49 (m, 1H), 4.13 (d, 2H). Ion spray MS $[M+1]^+ = 370$.

EXAMPLE 324

Compound 324

(E)-5-Pyridin-2-yl-thiophene-2-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide ditrifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and 5-pyridin-2-yl-thiophene-2-carboxylic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.97 (bs, 1H), 8.50 (m, 2H), 7.87 (m, 3H), 7.70 (m, 2H), 7.55 (dd, 1H), 7.30 (m, 1H), 6.89 (m, 2H), 6.47 (m, 1H), 4.15 (d, 2H). Ion spray MS $[M+1]^+ = 379$, $[M+2]^{2+} = 190$.

EXAMPLE 325

Compound 325

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(1-oxy-pyridin-4-yl)-benzamide ditrifluoroacetate.

A. 4-(1-Oxy-pyridin-4-yl)-benzoic acid.

4-Pyridin-4-yl-benzoic acid methyl ester (0.32 g, 1.6 mmol) in CH_2Cl_2 (30 ml) is treated with MCPBA (50-60%, 0.88 g) at 0 °C, and stirred at room temperature for 3 h. The reaction is quenched with 1 N NaOH; the CH_2Cl_2 layer is washed with H_2O, dried and concentrated to a give solid 4-(1-oxy-pyridin-4-yl)-benzoic acid methyl ester (0.23 g, 1.0 mmol). This material is treated with 1 N NaOH (1 ml) in MeOH/THF/H_2O (1 ml/1 ml/3 ml) at room temperature for 3 h, then neutralized with 1N HCl to pH ~ 6. The off-white solid is collected and washed with acetone to give 4-(1-oxypyridin-4-yl)-benzoic acid (0.12 g, 0.56 mmol). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (d, 2H), 8.0 (d, 2H), 7.88 (d, 2H), 7.83 (d, 2H).

B. (E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(1-oxy-pyridin-4-yl)-benzamide ditrifluoroacetate.

The title compound is prepared from (E)-3-(3-aminopropenyl)-4-(2-methoxy-ethoxymethoxy) benzonitrile and 4-(1-oxypyridin-4-yl)-benzoic acid essentially as described in EXAMPLE 307, Part D. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.98 (bs, 1H), 8.50 (bs, 1H), 8.42 (d, 2H), 8.02 (d, 2H), 7.95-7.88 (m, 5H), 7.56 (dd, 1H), 6.94 (d, 1H), 6.88 (d, 1H), 6.50 (m, 1H), 4.18 (d, 2H). APCI MS, $[M+H]^+ = 389$.

EXAMPLE 326

Compound 326

Biphenyl-4-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-propyl]-amide trifluoroacetate.

(E)-biphenyl-4-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide trifluoroacetate (0.006, 0.0012 mmol), prepared as described in EXAMPLE 315, is dissolved in methanol (5 mL), treated with a catalytic amount of 10% palladium on carbon and stirred under an atmosphere of hydrogen gas overnight. The solid is removed by filtration; the filtrate is concentrated by a stream of nitrogen. The residue is subjected to HPLC purification eluting with a gradient of 10% MeCN/H_2O (0.1% TFA) to 100% MeCN. Lyophylization of the appropriate fraction yields the title compound as a white solid (0.006 g, 0.012 mmol). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.90 (d, 2H), 7.70-7.60 (m, 5H), 7.54-7.35 (m, 4H), 6.90 (d, 1H), 3.43 (t, 2H), 2.75 (t, 2H), 1.97 (m, 2H). APCI MS $[M+1]^+ = 374$.

In a like manner, by the method described in EXAMPLE 326, the compounds of EXAMPLES 327-332 are prepared:

EXAMPLE 327

Compound 327

N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate.

The title compound is prepared from reduction of (E)-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.93 (bs, 1H), 8.50 (m, 2H), 8.00 (d, 1H), 7.90 (d, 2H), 7.68 (d, 2H), 7.64 (d, 1H), 7.55 (dd, 1H), 6.92 (d, 2H), 3.97 (s, 3H), 3.44 (t, 2H), 2.76 (t, 2H), 1.97 (m, 2H). APCI MS $[M+1]^+ = 405$.

EXAMPLE 328

Compound 328

Biphenyl-3,4'-dicarboxylic acid 3-amide 4'-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)- propyl]-amide} trifluoroacetate.

The title compound is prepared from reduction of (E)-biphenyl-3,4'-dicarboxylic acid 3-amide 4'-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)- allyl]-amide} trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.17 (s, 1H), 7.94-7.76 (m, 6H), 7.65-7.52 (m, 3H), 6.92 (d, 1H), 3.44 (t, 2H), 2.75 (t, 2H), 1.97 (m, 2H). APCI MS $[M+1]^+ = 417$.

EXAMPLE 329

Compound 329

4-tert-Butyl-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-propyl]-benzamide trifluoroacetate.

The title compound is prepared from reduction of (E)-4-tert-butyl-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-benzamide trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.74 (d, 2H), 7.60 (d, 1H), 7.50 (m, 3H), 6.89 (d, 1H), 3.39 (t, 2H), 2.74 (t, 2H), 1.94 (m, 2H), 1.33 (s, 9H). APCI MS $[M+1]^+ = 354$.

EXAMPLE 330

Compound 330

[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(3H-imidazol-4-yl)-benzamide ditrifluoroacetate.

The title compound is prepared from reduction of (E)-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(3H-imidazol-4-yl)-benzamide ditrifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.97 (s, 1H), 8,65 (t, 1H), 7.99 (m, 3H), 7.84 (d, 2H), 7.64 (d, 1H), 7.57 (dd, 1H), 6.93 (d, 1H), 3.44 (m, 2H), 2.76 (t, 2H), 1.98 (m, 2H). APCI MS $[M+1]^+ = 364$.

EXAMPLE 331

Compound 331

N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(1H-imidazol-2-yl)-benzamide ditrifluoroacetate.

The title compound is prepared from reduction of (E)-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(1H-imidazol-2-yl)-benzamide ditrifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.77 (t, 1H), 8.06 (m, 4H), 7.69 (s, 2H), 7.65 (d, 1H), 7.57 (dd, 1H), 6.93 (d, 1H), 3.44 (m, 2H), 2.76 (t, 2H), 1.97 (m, 2H). APCI MS $[M+1]^+ = 364$.

EXAMPLE 332

Compound 332

5-Pyridin-2-yl-thiophene-2-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide ditrifluoroacetate.

The title compound is prepared from reduction of (E)-5-pyridin-2-yl-thiophene-2-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide ditrifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.92 (bs, 1H), 8.50 (m, 2H), 7.90 (m, 2H), 7.68 (m, 2H), 7.60 (d, 1H), 7.54 (dd, 1H), 7.34 (m, 1H), 6.89 (d, 1H), 3.38 (t, 2H), 2.76 (t, 2H), 1.97 (m, 2H). APCI MS $[M+1]^+ = 381$.

EXAMPLE 333

Compound 333

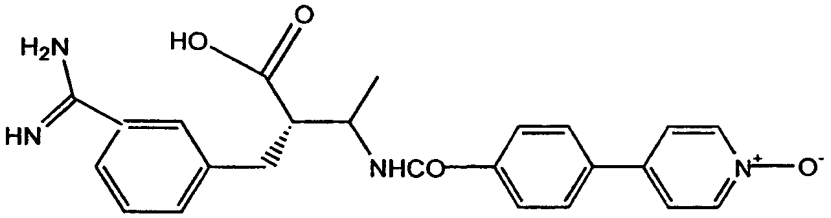
N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-piperidin-4-yl-benzamide ditrifluoroacetate.

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-pyridin-4-yl-benzamide ditrifluoroacetate is treated as described in EXAMPLE 326 then subjected to 50 psi of hydrogen gas for 5 hours in the presence of 10% Pd/C. The title compound (0.005 g, 0.008 mmol) is obtained by filtration and concentration of the filtrate to dryness. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.50 (bs, 1H), 7.80 (d, 2H), 7.59 (d, 1H), 7.55 (dd, 1H), 7.37 (d, 2H), 6.93 (d, 1H), 3.5-2.9 (m, 7H), 2.75 (t, 2H), 2.1-1.9 (m, 6H). Ion spray MS $[M+1]^+ = 381$, $[M+2]^{2+} = 191$.

EXAMPLE 334

Compound 334

2-(3-Carbamimidoyl-benzyl)-3-[4-(1-oxy-pyridin-4-yl)-benzoylamino]-butyric acid trifluoroacetate.

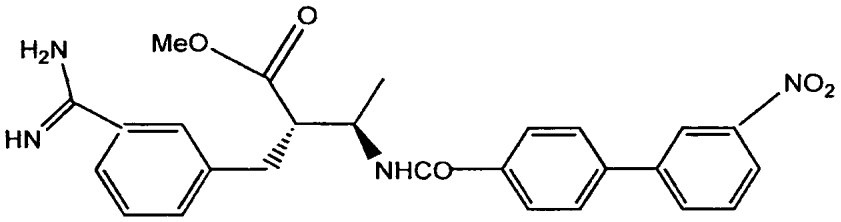


2-(3-Carbamimidoyl-benzyl)-3-[4-(1-oxy-pyridin-4-yl)-benzoylamino]-butyric acid methyl ester hydrochloride (0.60 g, 1.1 mmol) is dissolved in 15% MeCN/H_2O and treated with 1.0 N NaOH (6 ml). The mixture is stirred for 2 h at room temperature, and then acidified with TFA. The crude product is purified by HPLC eluting in a gradient of 10% MeCN/H_2O (0.1% TFA) to 100% MeCN. The product fractions are lyophilized to provide the title compound as a white solid (0.43 g, 0.92 mmol). ^{1}H NMR (DMSO-D_6, 300 MHz) δ 9.25 (s, 2H), 9.0 (s, 2H), 8.38 (d, 1H), 8.28 (d, 2H), 7.92-7.80 (m, 5H), 7.60-7.46 (m, 4H), 4.40 (m, 1H), 2.94 (m, 3H), 1.23 (d, 3H). Fab MS, $[M+H]^+ = 433$.

Example 335

Compound 335

2-(R)-(3-Carbamimidoylbenzyl)-3-(R)-[(3'-nitrobiphenyl-4-carbonyl)amino]-butyric acid methyl ester trifluoroacetate.

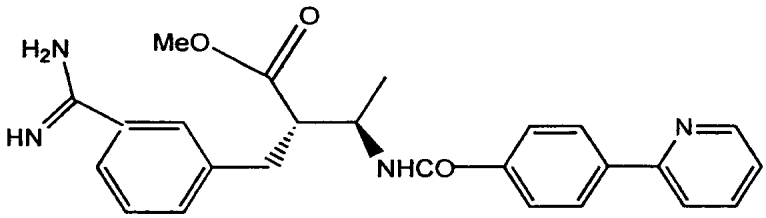


2-(R)-(3-Carbamimidoylbenzyl)-3-(R)-[(3'-nitrobiphenyl-4-carbonyl)amino]-butyric acid methyl ester trifluoroacetate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.40-8.52 (m, 2H), 8.15-8.30 (m, 2H), 7.85-8.0 (m, 4H), 7.75-7.82 (m, 1H), 7.52 (s, 1H), 4.35-4.51 (m, 1H), 3.47 (s, 3H), 3.04-3.15 (m, 1H), 2.90-3.03 (m, 2H), 1.23 (d, 3H). Ion Spray MS, $[M+H]^+ = 490$.

EXAMPLE 336

Compound 336

2(R)-3-Carbamimidoyl-benzyl)-3(R)-(4-pyridin-2-yl-benzoylamino)-butyric acid methyl ester ditrifluoroacetate.

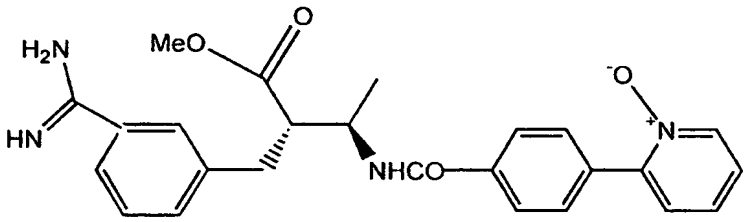


2(R)-3-Carbamimidoyl-benzyl)-3(R)-(4-pyridin-2-yl-benzoylamino)-butyric acid methyl ester ditrifluoroacetate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.68 (d, 1H), 7.92-8.11 (m, 6H), 7.47-7.68 (m, 5H), 4.40-4.55 (m, 1H), 3.62 (s, 3H), 3.02-3.18 (m, 3H), 1.32 (d, 3H). Ion spray MS $[M+1]^+ = 431$.

EXAMPLE 337

Compound 337

2(R)-(3-Carbamimidoyl-benzyl)-3(R)-[4-(1oxy-pyridin-2-yl)-benzoylamino]-butyric acid methyl ester-trifluoroacecate.

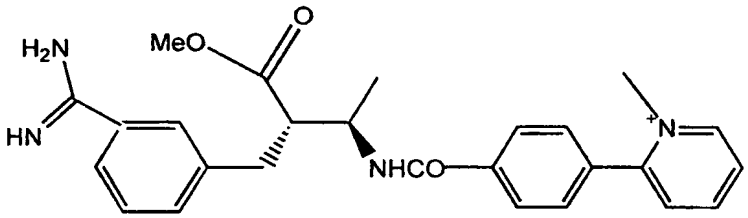


2(R)-(3-Carbamimidoyl-benzyl)-3(R)-[4-(1oxy-pyridin-2-yl)-benzoylamino]-butyric acid methyl ester-trifluoroacecate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (CD_3OD, 300 Mhz) δ 8.46 (d, 1H), 7.92 (m, 4H), 7.67-7.77 (m, 2H), 7.45-7.66 (m, 5H), 4.40-4.55 (m, 1H), 3.60 (s, 3H), 3.02-3.18 (m, 3H), 1.34 (d, 3H). Ion spray MS $[M+1]^+ = 447$.

EXAMPLE 338

Compound 338

2-{4-[3-(3-Carbamimidoyl-phenyl)-2(R)-methoxycarbonyl-1(R)-methyl-propylcarbamoyl]-phenyl}-1-methyl-pyridinium-ditrifluoroacetate.

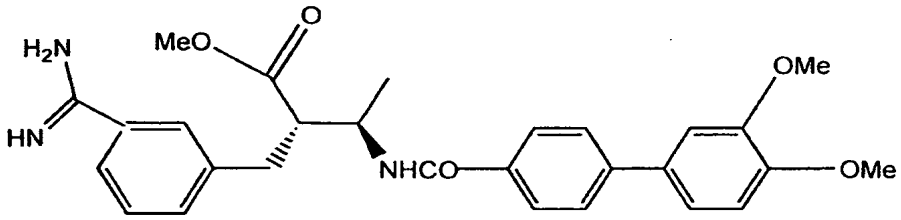


2-{4-[3-(3-Carbamimidoyl-phenyl)-2(R)-methoxycarbonyl-1(R)-methyl-propylcarbamoyl]-phenyl}-1-methyl-pyridinium-ditrifluoroacetate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (CD_3OD, 300 Mhz) δ 9.04 (d, 1H), 8.66 (m, 1H), 8.02-8.18 (m, 4H), 7.79 (d, 2H), 7.45-7.70 (m, 4H), 4.38-4.50 (m, 1H), 4.22 (s, 3H), 3.60 (s, 3H), 3.03-3.18 (m, 3H), 1.38 (s, 3H). Fab MS $[M+]^+ = 445$.

EXAMPLE 339

Compound 339

2-(R)-(3-Carbamimidoylbenzyl)-3-(R)-[(3',4'-dimethoxybiphenyl-4-carbonyl)amino]-butyric acid methyl ester trifluoroacetate.

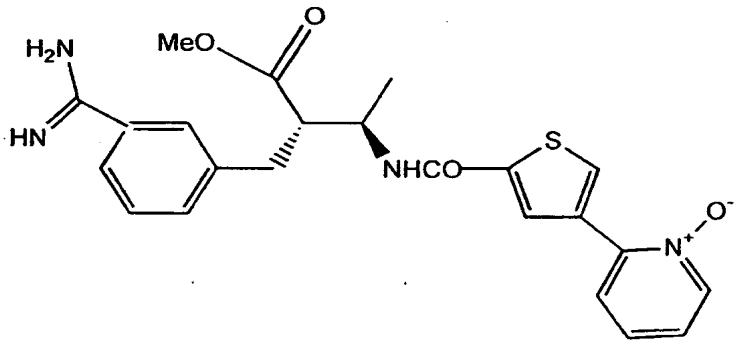


2-(R)-(3-Carbamimidoylbenzyl)-3-(R)-[(3',4'-dimethoxybiphenyl-4-carbonyl)amino]-butyric acid methyl ester trifluoroacetate is prepared by procedures substantially similar to those used to prepare compound 216, starting from the appropriate materials. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.32 (d, 1H), 7.82-7.9 (m, 2H), 7.71-7.78 (m, 2H), 7.61 (s, 1H), 7.52 (m, 2H) 7.22-7.30 (m, 2H), 7.06 (d, 1H) 4.08-4.35 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.50 (s, 3H), 3.03-3.13 (m, 1H), 2.92-3.02 (m, 2H), 1.25 (d, 3H). Ion Spray MS, $[M+H]^+ = 490$.

EXAMPLE 340

Compound 340

2-(R)-(3-Carbamimidoyl-benzyl)-3(R)-{[4-(1-oxy-pyridin-2-yl)-thiophene-2-carbonyl]-amino}-butyric acid methyl ester trifluoroacetate.

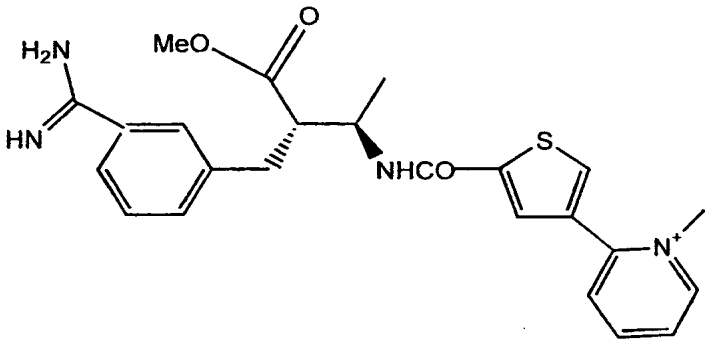


2-(R)-(3-Carbamimidoyl-benzyl)-3(R)-{[4-(1-oxy-pyridin-2-yl)-thiophene-2-carbonyl]-amino}-butyric acid methyl ester trifluoroacetate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (CD_3OD, 300 Mhz) δ 8.73 (s, 1H), 8.42 (d, 1H), 8.37 (m, 2H), 7.92-7.98 (m, 1H), 7.42-7.68 (m, 5H), 4.35-4.48 (m, 1H), 3.60 (s, 3H), 3.01-3.20 (m, 3H), 1.32 (d, 3H), Ion spray MS $[M+1]^+ = 453$.

EXAMPLE 341

Compound 341

2-{5-[3-(3-Carbamimidoyl-phenyl-2(R)-methoxycarbonyl-1(R)-methyl-propylcarbamoyl]-thiophen-3-yl}-1-methyl-pyridinium ditrifluoroacetate.

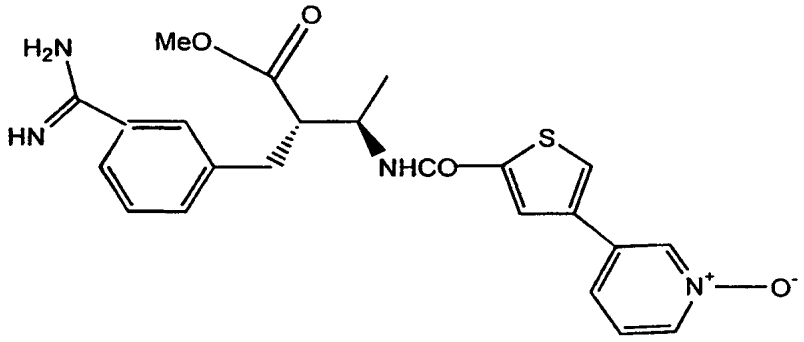


2-{5-[3-(3-Carbamimidoyl-phenyl-2(R)-methoxycarbonyl-1(R)-methyl-propylcarbamoyl]-thiophen-3-yl}-1-methyl-pyridinium ditrifluoroacetate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (CD_3OD, 300 Mhz) δ 8.99 (d, 1H), 8.60 (m, 1H), 8.28 (s, 1H), 8.02-8.17 (m, 3H), 7.45-7.68 (m, 4H), 4.38-4.50 (m, 1H), 4.32 (s, 3H), 3.55 (s, 3H), 3.02-3.15 (m, 3H), 1.34 (d, 3H). Fab MS $[M+]^+ = 451$.

EXAMPLE 342

Compound 342

2-(R)-(3-Carbamimidoylbenzyl)-3-(R)-{oxypyridin-3yl)-thiophene-2-carbonyl}-amino}butyric acid methyl ester trifluoroacetate.

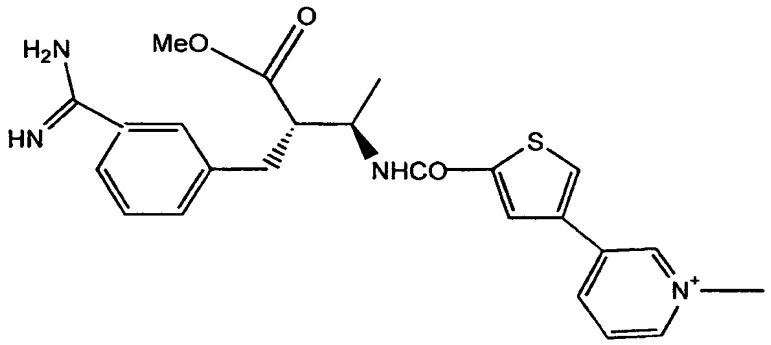


2-(R)-(3-Carbamimidoylbenzyl)-3-(R)-{oxypyridin-3yl)-thiophene-2-carbonyl}-amino}butyric acid methyl ester trifluoroacetate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.67 (s, 1H), 8.36 (d, 1H), 8.30 (dd, 1H), 8.21 (s, 1H), 8.12 (s, 1H), 7.93 (dd, 1H), 7.45-7.68 (m, 4H), 4.37-51 (m, 1H), 3.61 (s, 3H), 3.02-3.18 (m, 3H), 1.32 (d, 3H). Ion Spray MS, $[M+ H]^+ = 453$.

EXAMPLE 343

Compound 343

3-{5-[3-(3-Carbamimidoylphenyl)-2-(R)-methoxycarbonyl-1-(R)-methyl-propylcarbamoyl]-thiophen-3-yl}-1-methylpyridinium ditrifluoroacetate.



3-{5-[3-(3-Carbamimidoylphenyl)-2-(R)-methoxycarbonyl-1-(R)-methyl-propylcarbamoyl]-thiophen-3-yl}-1-methylpyridinium ditrifluoroacetate is prepared by procedures substantially similar to those described above, starting from appropriate materials. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.34 (s, 1H), 8.80-8.88 (m, 2H), 8.36 (s, 1H), 8.25 (s, 1H), 8.09-8.17 (m, 1H), 7.48-7.68 (m, 4H), 4.46 (s, 3H), 4.37-4.45 (m, 1H), 3.58 (s, 3H), 3.02-3.18 (m, 3H), 1.33 (d, 3H). Ion Spray MS, M^+ = 451.

EXAMPLE 344

Compound 344

2-(R)-(3-Carbamimidoyl-benzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester trifluoroacetate.

A. 4-(6-methoxy-pyridin-3-yl)-benzoic acid ethyl ester.

A 1.6 M solution of nBuLi in hexane (9.53 mL, 15.24 mmol) is added dropwise to a stirred solution of 5-Bromo-2-methoxy-pyridine (2.72 g, 14.52 mmol) in THF (50 mL) at -78°C. The resulting mixture is stirred for 15 minutes at -78°C. To this is added a 0.5 M solution of $ZnCl_2$ in THF (29.04 mL, 14.52 mmol) and the resulting mixture allowed to warm to room temperature.

In a separate flask tetrakis(triphenylphosphine)palladium(0) (0.58g, 0.50 mmol) is stirred in THF (10 mL). To this is added 4-ethyl-iodobenzoate (3.61g, 13.07 mmol). The contents of the two flasks are combined and stirred for 1 hour at room temperature. A 5% solution of ammonia in water (150 mL) is added with stirring. The mixture is extracted with EtOAc (3X). The organics are combined and dried over $MgSO_4$, filtered and concentrated. The crude product is purified by flash chromatography (2.5% EtOAc/hexane to 5% EtOAc/hexane) to give the product as a white solid (2.43g, 9.44 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz) d 8.41 (d, 1H), 8.08 (d, 2H), 7.82 (dd, 1H), 7.60 (d, 2H), 6.82 (d, 1H), 4.38 (q, 2H), 3.98 (s, 3H), 1.40 (t, 3H).

B. 4-(6-methoxy-pyridin-3-yl)-benzoic acid.

A 1N sodium hydroxide solution (20 mL) is added to a mixture of 4-(6-methoxy-pyridin-3-yl)-benzoic acid ethyl ester (2.43g, 9.44 mmol) in MeOH (20 mL) and THF (20 mL) and stirred at 35 °C for 1 hour. The reaction is cooled and 1N HCl added until the pH is ~4. The precipitate is isolated by filtration and dried in a vacuum desiccator to give a the product as a white solid (2.03g, 8.86 mmol). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.57 (d, 1H), 8.08 (dd, 1H), 7.99 (d, 2H), 7.82 (d, 2H), 6.95 (d, 1H), 3.89 (s, 3H).

C. 2-(R)-(3-Cyano-benzyl)-3(R)-[4-(6-methoxy-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester.

To a stirred solution of 4-(6-methoxy-pyridin-3-yl)-benzoic acid (0.67g, 2.54 mmol) in DMF (5 mL) is added DIPEA (0.44mL, 2.54 mmol), TBTU (0.91g, 2.54mmol) and 2(R)-(3-Cyano-benzyl)-3(R)-amino-butyric acid methyl ester (0.59g, 2.54 mmol). The solution is stirred overnight at room temperature. The reaction is diluted with EtOAc and washed with saturated sodium bicarbonate (3X), brine, dried over $MgSO_4$, filtered and concentrated. The crude product is purified by flash chromatography (50% EtOAc/hexane to 60% EtOAc/hexane) to give the product as a white solid (0.83g, 1.87 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (d, 1H), 7.92 (d, 2H), 7.83 (dd, 1H), 7.63 (d, 1H), 7.30-7.55 (m, 4H), 6.87 (d, 1H), 4.42-4.53 (m, 1H), 3.98 (s, 3H), 3.66 (s, 3H), 2.85-3.08 (m, 3H), 1.28 (d, 3H).

D. 2-(R)-(3-Cyano-benzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester.

A mixture of 2-(R)-(3-Cyano-benzyl)-3(R)-[4-(6-methoxy-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester (0.80g, 1.805 mmol) and pyridine hydrochloride (3.37g, 21.6 mmol) is heated for 10 minutes at 160 °C. The reaction is cooled to room temperature and water added (40 mL). The resulting mixture is partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer is washed with saturated sodium bicarbonate (2X), brine, dried over $MgSO_4$, filtered and concentrated to give the crude product as a tan foam (0.82g). ^{1}H NMR ($CDCl_3$, 300 Mhz) δ 7.78-7.95 (m, 3H), 7.65-7.73 (m, 1H), 7.28-7.57 (m, 6H), 6.45 (d, 1H), 4.41-4.54 (m, 1H), 3.66 (s, 3H), 2.82-3.07 (m, 3H), 1.28 (d, 3H).

E. 2-(R)-(3-Carbamimidoyl-benzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester-trifluoroacetate.

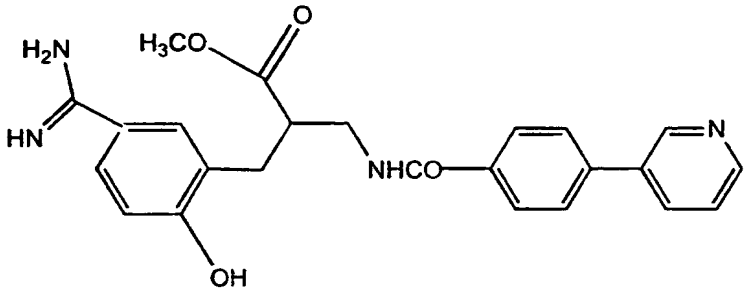
This compound is prepared by procedures substantially similar to those described above, starting with 2-(R)-(3-Cyano-benzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.32 (d, 1H), 7.88 (d, 1H), 7.81-7.83 (m, 2H), 7.65-7.69

(m, 2H), 7.55-7.63 (m, 2H), 7.45-7.52 (m, 2H), 6.45 (d, 1H), 4.32-4.48 (m, 1H), 3.48 (s, 3H), 3.01-3.11 (m, 1H), 2.88-2.98 (m, 2H), 1.22 (d, 3H). Ion spray MS $[M+1]^+ = 447$.

EXAMPLE 345

Compound 345

2-(5-Carbamimidoyl-2-hydroxy-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino-propionic acid methyl ester.



A. 3-(4-(Pyridin-3-yl)-benzoylamino)-propionic acid *t*-butyl ester.

To a suspension of 4-(pyridin-3-yl)-benzoic acid (1.32g, 6.6 mmol) in CH_2Cl_2 (26 mL) is added DMF (8 ml, 0.5 mmol) followed by oxalyl chloride (6.6 mL, 2M in CH_2Cl_2). The resulting suspension is stirred for 3 hr then concentrated under vacuum. To this residue is added *t*-butyl-(3-amino)-propionionate hydrochloride (1.089g, 6 mmol). This mixture is diluted with CH_2Cl_2 (26 mL) cooled to 0 °C then Et_3N added (3.3 mL, 24 mmol). The resulting mixture is stirred for 3 hr. then diluted with ethyl acetate:CH_2Cl_2 (approx. 2:1), washed with water (3x), then brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (60% ethyl acetate in CH_2Cl_2 to give 1.22g of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.59 (t, J = 7Hz, 2H), 3.73 (q, J = 7Hz, 2H), 6.98 (bt, J = 7Hz, 1H), 7.40 (m, 1H), 7.67 (d, J = 8Hz, 2H), 7.89 (m, 3H), 8.63 (bd, 1H), 8.88 (bs, 1H). MS m/z 327 (M+H).

B. 2-(5-Iodo-2-(2-methoxy-ethoxymethoxy)-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino)-propionic acid *t*-butyl ester.

To a cooled (-15°C) solution of diisopropylamine (1.6 mL, 11.5 mmol) in THF (20 mL), is added dropwise *n*-BuLi (4.6 mL, 2.5 M in hexanes). The resulting solution is stirred for 10 min then cooled to -78 °C over 10 min. To this solution is added a solution of 3-(4-(pyridin-3-yl)-benzoylamino)-propionic acid *t*-butyl ester. (1.65g, 5 mmol) in THF / DMPU (6 mL, 1/1). On complete addition, the reaction mixture is warmed to -40 °C over 15 min. To this solution is added a solution of bromide (2.13g, 5.3 mmol) in THF (10 mL). The reaction mixture is stirred for 20 min then HCl (5ml, 1M) added. This mixture is diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 80% ethyl acetate in hexanes) to give

3.03g of the title compound as a foam. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.81 (m, 1H), 2.95 (m, 1H), 3.06 (m,1H), 3.47 (s, 3H), 3.54 (m, 2H), 3.68 (m, 2H), 3.80 (m, 2H), 5.29 (s, 2H), 6.91 (m, 2H), 7.40 (m, 1H), 7.47 (m, 2H), 7.66 (d, J = 8Hz, 2H), 7.89 (m, 2H), 8.64 (bd, 1H), 8.88 (bs, 1H). MS m/z 647 (M+H).

C. 2-(5-Iodo-2-hydroxy-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino-propionic acid methyl ester.

To a solution of 2-(5-iodo-2-(2-methoxy-ethoxymethoxy)-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino)-propionic acid *t*-butyl ester (3.03g, 4.69 mmol) in CH_2Cl_2 (25 mL) is added TFA (5 mL). The resulting solution is stirred for 19 hr then concentrated to approx. half the original volume. To this solution is added toluene (20 mL). This solution is concentrated under reduced pressure. The residue is dissolved in THF (20 mL) and cooled to -10 °C. To this solution is added NaOMe (2.3 mL, 25% wt in MeOH). After stirring 10 min. the reaction mixture is brought to pH 6 with hydrochloric acid (1 M). This mixture is diluted with ethyl acetate, washed with water and brine. dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 80% ethyl acetate in hexanes) to give 2.13g of the title compound. ^{1}H NMR ($CDCl_3$) δ 3.01 (m, 3H), 3.68 (m, 2H), 3.70 (s, 3H), 6.67 (d, J = 8Hz, 1H), 7.39 (m, 3H), 7.48 (d, J = 8Hz, 2H), 7.85 (m, 3H), 8.6 (dd, 1H), 8.70 (d, 1H), 9.40 (bs, 1H). MS m/z 517 (M+H).

D. 2-(5-cyano-2-hydroxy-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino-propionic acid methyl ester.

To a mixture of 2-(5-iodo-2-hydroxy-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino)-propionic acid methyl ester (2.1g, 4.07 mmol) $(Ph_3P)_4Pd$ (460 mg, 0.4 mmol) and $ZnCN_2$ (1.42g, 12.2 mmol) is added DMF (20 mL). The resulting mixture is degassed and purged with argon then placed in an oil bath held at 73 °C. The reaction mixture is stirred at this temperature for 90 min. then cooled diluted with ethyl acetate and washed with water. The aqueous fraction is extracted with ethyl acetate:CH_2Cl_2 (4:1, 3x). The combined organic extract is dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (eluting with 90% ethyl acetate in CH_2Cl_2) to give 1.53g of the title compound. ^{1}H NMR ($CDCl_3$) δ 3.03 (m, 1H), 3.16 (m, 1H), 3.68 (m, 3H), 3.70 (s, 3H), 6.93 (d, J = 8Hz, 1H), 7.39 (m, 3H), 7.50 (d, J = 8Hz, 2H), 7.95 (m, 3H), 8.6 (dd, 1H), 8.71 (d, 1H). MS m/z 416 (M+H).

E. 2-(5-Carbamimidoyl-2-hydroxy-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino-propionic acid methyl ester.

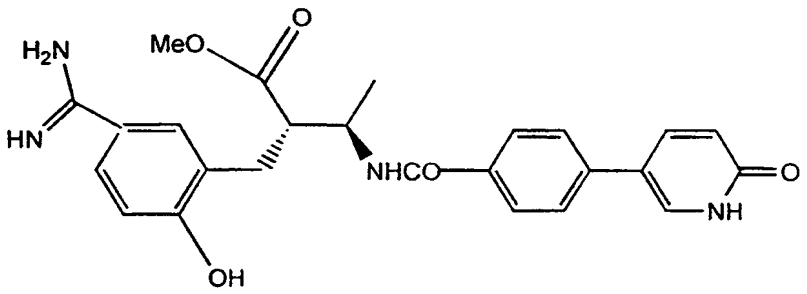
2-(5-cyano-2-hydroxy-benzyl)-3-(4-(pyridin-3-yl)-benzoylamino-propionic acid methyl ester (623mg, 1.5 mmol) is dissolved in a saturated solution of HCl in methanol (15 mL). This solution is stirred for 5 hr. then concentrated under reduced pressure. The residue is taken up in a saturated solution of NH_3 in MeOH (10 mL) and stirred for 18 hr then concentrated under reduced pressure. The residue is

purified by flash chromatography (eluting with 1% Et_3N / 10% EtOAc in CH_2Cl_2) to give 343 mg of the title compound as a solid. ^1H NMR (CD_3OD) δ 2.88 (m, 1H), 3.08 (m, 2H), 3.50 (m, 1H), 3.67 (s, 3H), 3.68 (m, 1H), 6.68 (d, J = 8Hz, 1H), 7.50 (m, 3H), 7.78 (d, J = 8Hz, 2H), 8.0 (d, J = 8Hz, 2H), 8.14 (m, 1H), 8.55 (d, 1H), 8.86 (bs, 1H). MS m/z 433 (M+H).

EXAMPLE 346

Compound 346

2(R)-(3-Carbamimidoyl-6-hydroxybenzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester



By the methods described above is prepared 2(R)-(3-Carbamimidoyl-6-hydroxybenzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester.

The molecules described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme in the coagulation cascade, factor Xa, rather than thrombin. Both free factor Xa and factor Xa assembled in the prothrombinase complex (Factor Xa. Factor Va, calcium and phospholipid) are inhibited. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-

term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

These compounds may be used alone or in combination with other diagnostic, anticoagulant, antiplatelet or fibrinolytic agents. For example adjunctive administration of factor Xa inhibitors with standard heparin, low molecular weight heparin, direct thrombin inhibitors (i.e. hirudin), aspirin, fibrinogen receptor antagonists, streptokinase, urokinase and/or tissue plasminogen activator may result in greater antithrombotic or thrombolytic efficacy or efficiency. The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates including humans, sheep, horses, cattle, pigs, dogs, rats and mice. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any factor Xa inhibitor can be added to or contacted with any medium containing or suspected of containing factor Xa and in which it is desired that blood coagulation be inhibited.

In addition to their use in anticoagulant therapy, factor Xa inhibitors may find utility in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a pathologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor. Inhibition of factor Xa will effectively block thrombin generation and therefore neutralize any pathologic effects of thrombin on various cell types.

Accordingly, the invention provides a method of inhibiting factor Xa comprising contacting a factor Xa inhibitory amount of a compound of formula I with a composition containing Factor Xa. According to a further feature of the invention there is provided a method of inhibiting the formation of thrombin comprising contacting Factor Xa inhibitory amount of a compound of formula I with a composition containing Factor Xa.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa, for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of formula I or a composition containing a compound of formula I. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting Factor Xa and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of Formula I in association with a pharmaceutically acceptable carrier or coating.

In practice compounds of the present invention may generally be administered parenterally, intravenously, subcutaneously intramuscularly, colonically, nasally, intraperitoneally, rectally or orally.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or

subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

The compounds of the present invention may also be formulated for use in conjunction with other therapeutic agents such as agents or in connection with the application of therapeutic techniques to address pharmacological conditions which may be ameliorated through the application of a compound of formula I, as described herein.

The compounds of the present invention may be used in combination with any anticoagulant, antiplatelet, antithrombotic or fibrinolytic agent. Often patients are concurrently treated prior, during and after interventional procedures with agents of these classes either in order to safely perform the

interventional procedure or to prevent deleterious effects of thrombus formation. Some examples of classes of agents known to be anticoagulant, antiplatelet, antithrombotic or profibrinolytic agents include any formulation of heparin, low molecular weight heparins, pentasaccharides, fibrinogen receptor antagonists, thrombin inhibitors, Factor Xa inhibitors, or Factor VIIa inhibitors.

The compounds of the present invention may be used in combination with any antihypertensive agent or cholesterol or lipid regulating agent, or concurrently in the treatment of restenosis, atherosclerosis or high blood pressure. Some examples of agents that are useful in combination with a compound according to the invention in the treatment of high blood pressure include compounds of the following classes: beta-blockers, ACE inhibitors, calcium channel antagonists and alpha-receptor antagonists. Some examples of agents that are useful in combination with a compound according to the invention in the treatment of elevated cholesterol levels or disregulated lipid levels include compounds known to be HMGCoA reductase inhibitors, compounds of the fibrate class,

It is understood that the present invention includes combinations of compounds of the present invention with one or more of the aforementioned therapeutic class agents

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature and below which tests results are believed to correlate to pharmacological activity in humans and other mammals.

Enzyme Assays:

The ability of the compounds in the present invention to act as inhibitors of factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasmin and activated protein C is evaluated by determining the concentration of inhibitor which resulted in a 50% loss in enzyme activity (IC50) using purified enzymes.

All enzyme assays are carried out at room temperature in 96-well microtiter plates using a final enzyme concentration of 1 nM. The concentrations of factor Xa and thrombin are determined by active site titration and the concentrations of all other enzymes are based on the protein concentration supplied by the manufacturer. Compounds according to the invention are dissolved in DMSO, diluted with their respective buffers and assayed at a maximal final DMSO concentration of 1.25%. Compound dilutions are added to wells containing buffer and enzyme and pre-equilibrated for between 5 and 30 minutes. The enzyme reactions are initiated by the addition of substrate and the color developed from the hydrolysis of the peptide-p-nitroanilide substrates is monitored continuously for 5 minutes at 405 nm on a Vmax microplate reader (Molecular Devices). Under these conditions, less than 10% of the substrate is utilized in all assays. The initial velocities measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the control velocity (IC50). The apparent Ki values are then determined according to the Cheng-Prusoff equation (IC50 = Ki [1+[S]/Km]) assuming competitive inhibition kinetics.

An additional *in vitro* assay may be used to evaluate the potency of compounds according to the invention in normal human plasma. The activated partial thromboplastin time is a plasma-based clotting assay that relies on the *in situ* generation of factor Xa, its assembly into the prothrombinase complex and the subsequent generation of thrombin and fibrin which ultimately yields the formation of a clot as the assay endpoint. This assay is currently used clinically to monitor the *ex vivo* effects of the commonly used anticoagulant drug heparin as well as direct acting antithrombin agents undergoing clinical evaluation. Therefore, activity in this *in vitro* assay is considered as a surrogate marker for *in vivo* anticoagulant activity.

Human Plasma Based Clotting Assay:

Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A volume of 100 µl of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing 100 µl of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and placed in the instrument. Following a 3 minute warming period the instrument automatically adds 100 µl of activated cephaloplastin reagent (Actin, Dade) followed by 100 µl of 0.035 M $CaCl_2$ to initiate the clotting reaction. Clot formation is determined spectrophotometrically and measured in seconds. Compound potency is quantitated as the concentration required to double a control clotting time measured with human plasma in the absence of the compound according to the invention.

Compounds according to the invention may also be evaluated for their *in vivo* antithrombotic efficacy in two well established animal experimental models of acute vascular thrombosis. A rabbit model of jugular vein thrombosis and a rat model of carotid artery thrombosis are used to demonstrate the antithrombotic activity of these compounds in distinct animal model paradigms of human venous thrombosis and arterial thrombosis, respectively.

Experimental *In Vivo* Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI 1-161) in Experimental Venous Thrombosis-a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen and U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994). The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) *in vivo* generated at a site of injury and partial stasis in the jugular vein.

Male and female New Zealand white rabbits weighing 1.5-2 kg are anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of

1 mL/kg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 mL/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just proximal to the common jugular vein. A 1 cm segment of the vein is isolated with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp. This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled with 0.5 mL of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The vascular clamps are then removed, restoring blood flow through this portion of the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as the primary end point. Animals are maintained for an additional thirty minutes to obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and continued through the period of clot formation and maturation. Three blood samples (3 mL ea.) are obtained for evaluation of hemostatic parameters: one just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to vehicle treated control animals.

Experimental *In Vivo* Rat Arterial Thrombosis Model:

The antithrombotic efficacy of factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery $FeCl_2$-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22, 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model, R.J. Broersma,

L.W. Kutcher and E.F. Heminger. Thrombosis Research 64, 405-412 (1991). This model is widely used to evaluate the antithrombotic potential of a variety of agents including heparin and the direct acting thrombin inhibitors.

Sprague Dawley rats weighing 375-450 g are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4-0 silk sutures are placed around the vessel to facilitate instrumentation. An electromagnetic flow probe (0.95-1.0 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of parafilm is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 mm strip of filter paper previously saturated in 35% $FeCl_2$ is placed on top of the vessel downstream from the probe for ten minutes and then removed. The $FeCl_2$ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the $FeCl_2$-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained, the artery is ligated proximal and distal to the area of injury and the vessel is excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 mL of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to $FeCl_2$ application. The time between $FeCl_2$ application and the time at which carotid blood flow reached zero is recorded as time to occlusion (TTO). For vessels that did not occlude within 60 minutes, TTO is assigned a value of 60 minutes. Five minutes after application of $FeCl_2$, a second blood sample is drawn (B2). After 10 minutes of $FeCl_2$ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some instances a compound according to the invention may be administered orally. Rats are restrained

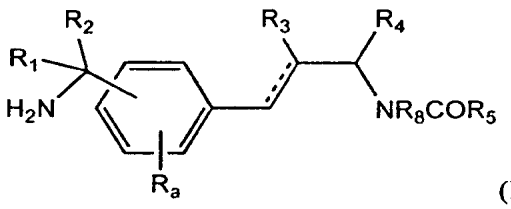
manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 mL/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then performed according to the protocol described above.

By way of example, Compound 184 shows K_i values of 27.0 nM, 1.72 μM, and 2.71 μM, in the Factor Xa, trypsin, and thrombin assays, respectively. Compound 45 shows K_i values of 94.0 nM, 129 nM, and 477 nM, in the Factor Xa, trypsin, and thrombin assays, respectively. Compound 167 shows K_i values of 19.0 nM, 46 nM, and 1.228 μM, in the Factor Xa, trypsin, and thrombin assays, respectively.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

WHAT IS CLAIMED IS:

1. A compound of the formula



(I)

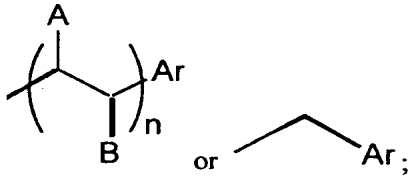
------ is a single or double bond;

R_a is hydrogen, hydroxy or amino:

R_1 and R_2 are hydrogen or taken together are $=NR_9$;

R_3 is hydrogen, $-CO_2R_6$, $-C(O)R_6$, $-CONR_6R_6$, $-CH_2OR_7$ or $-CH_2SR_7$;

R_4 is hydrogen, alkyl, Q-alkyl or thioheterocyclyl, or a group of formula



R5 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, aryl, fused cycloalkenylaryl, used cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, heteroaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl, fused heterocyclylheteroaryl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, aralkynyl or heteroaralkynyl;

R6 is hydrogen or lower alkyl;

R_7 is hydrogen, lower alkyl, Ar(lower alkyl), lower acyl, aroyl or heteroaroyl;

R_8 is hydrogen or lower alkyl;

R_9 is hydrogen, $R_{10}O_2C$-, $R_{10}O$-, HO-, cyano, $R_{10}CO$-, HCO-, lower alkyl, nitro, or $Y^{1a}Y^{2a}N$-;
R_{10} is alkyl, aralkyl, or heteroaralkyl;

Y^{1a} and Y^{2a} are independently hydrogen or alkyl;

A and B are hydrogen or taken together are a bond;

Q is R_7O- or R_7S- or Y^1Y^2N-;

Y^1 and Y^2 are independently hydrogen, alkyl, aryl, and aralkyl, or one of Y^1 and Y^2 is acyl or aroyl and the other of Y^1 and Y^2 is hydrogen, alkyl, aryl, and aralkyl;

Ar is aryl or heteroaryl; and

n is 0, 1 or 2; or

a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

2. The compound according to claim 1 wherein ------ is a single bond, or
a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

3. The compound according to claim 1 wherein ------ is a double bond, or
a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

4. The compound according to claim 1 wherein R_a is hydrogen, or
a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

5. The compound according to claim 1 wherein R_a is hydroxy or amino; more preferred is hydroxy, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

6. The compound according to claim 1 wherein R_1 and R_2 taken together are $=NR_9$, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

7. The compound according to claim 1 wherein R_1 and R_2 taken together are =NH, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

8. The compound according to claim 1 wherein R_3 is hydrogen, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

9. The compound according to claim 1 wherein R_3 is $-CO_2R_6$, $-C(O)R_6$, $-CH_2OR_7$ or $-CH_2SR_7$, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

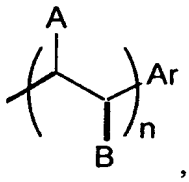
10. The compound according to claim 1 wherein R_3 is $-CO_2R_6$, $-CH_2OR_7$ or $-CH_2SR_7$, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

11. The compound according to claim 1 wherein R_3 is $-CO_2R_6$ or $-CH_2OR_7$, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

12. The compound according to claim 1 wherein R_3 is $-CO_2R_6$ and R_6 is lower alkyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

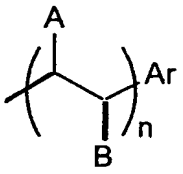
13. The compound according to claim 1 wherein R_3 is $-CH_2OR_7$ or $-CH_2SR_7$ and R_7 is hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

14. The compound according to claim 1 wherein R_4 is hydrogen, alkyl or Q-alkyl, or a group of formula



or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

15. The compound according to claim 1 wherein R_4 is lower alkyl or a group of formula



where A and B are hydrogen and n is 1, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

16. The compound according to claim 1 wherein R_4 is Q-alkyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

17. The compound according to claim 1 wherein R_4 is R_7O(lower alkyl)-, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

18. The compound according to claim 1 wherein R_4 is thioheterocyclyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

19. The compound according to claim 1 wherein R5 is alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused heteroarylcycloalkyl, fused arylcycloalkenyl, fused heteroarylcycloalkenyl, fused arylheterocyclyl, fused heteroarylheterocyclyl, fused arylheterocyclenyl, fused heteroarylheterocyclenyl, fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl, fused heterocyclylheteroaryl, aralkyl, heteroaralkyl, aralkenyl, heteroaralkenyl, aralkynyl or heteroaralkynyl; more preferred is fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclylaryl, fused heterocyclenylaryl, fused cycloalkylheteroaryl, fused cycloalkenylheteroaryl, fused heterocyclenylheteroaryl or fused heterocyclylheteroaryl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

20. The compound according to claim 1 wherein R5 is cycloalkyl, heterocyclyl, aralkyl or aralkynyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

21. The compound according to claim 1 wherein R5 is aryl or heteroaryl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

22. The compound according to claim 1 wherein R5 is phenyl, naphthyl, or heteroaryl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

23. The compound according to claim 1 wherein R5 is phenyl substituted phenyl, heteroaryl substituted phenyl, phenyl substituted heteroaryl or optionally heteroaryl substituted heteroaryl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

24. The compound according to claim 1 wherein R_6 is lower alkyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

25. The compound according to claim 1 wherein Q is R_7O-, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

26. The compound according to claim 1 wherein R_7 is hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

27. The compound according to claim 1 wherein R_7 is Ar(lower alkyl) or heteroaroyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

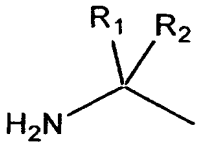
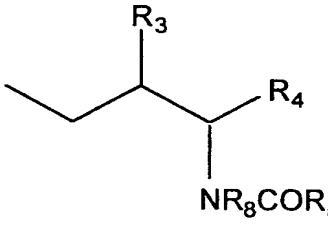
28. The compound according to claim 1 wherein R_8 is hydrogen, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

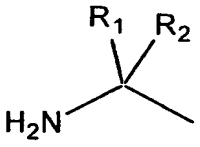
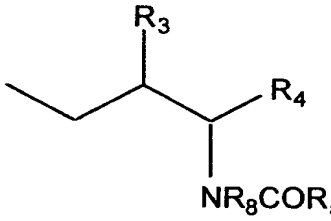
29. The compound according to claim 1 wherein R_9 is hydrogen, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

30. The compound according to claim 1 wherein A, B, R_8 and R_9 are hydrogen, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

31. The compound according to claim 1 wherein R_{10} is lower alkyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

32. The compound according to claim 1 wherein n is 1, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

33. The compound according to claim 1 wherein the  moiety is in the meta position to the position of attachment of the phenyl moiety to the  moiety, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

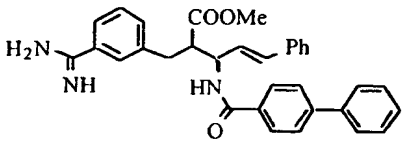
34. The compound according to claim 1 wherein R_a is hydroxy or amino, which is in the para position to the  moiety which is in the meta position to the position of attachment of the phenyl moiety to the  moiety, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

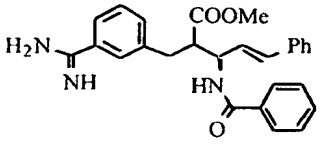
35. The compound according to claim 34 wherein R_a is hydroxy, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

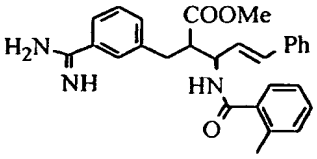
36. The compound according to claim 1 wherein Ar is aryl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

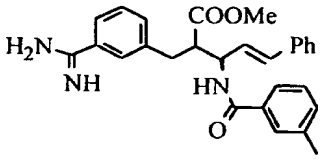
37. The compound according to claim 1 wherein Ar is phenyl, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

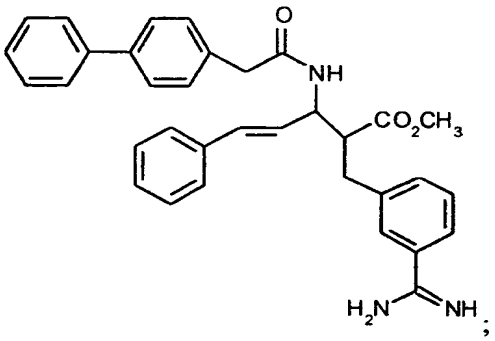
38. A compound according to claim 1 which is:

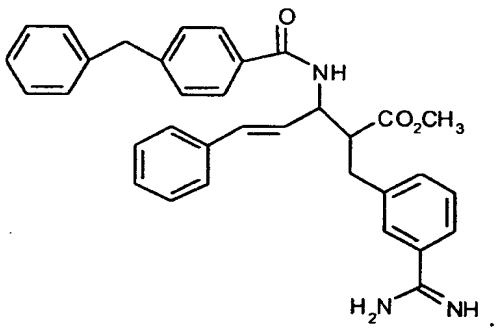

;

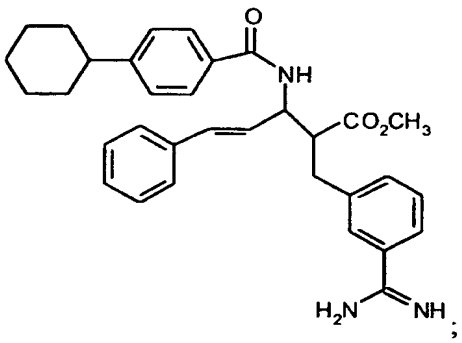

;

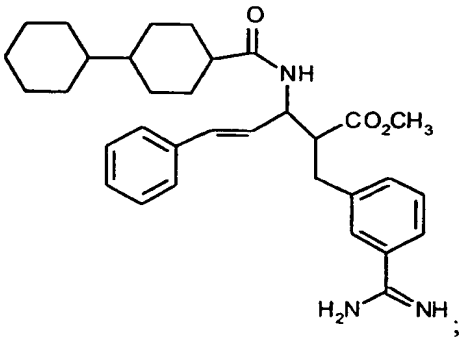

;

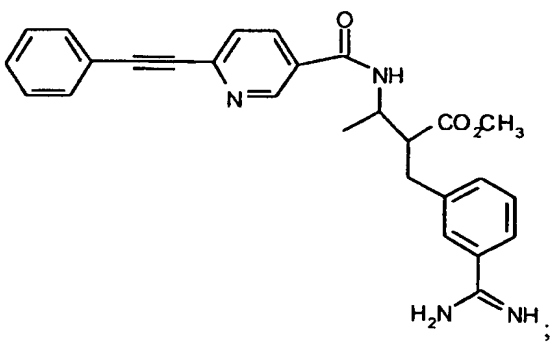

;

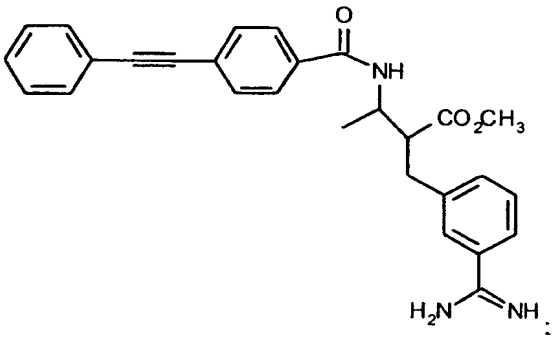

;

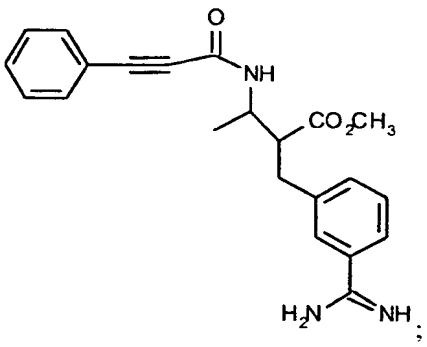

;

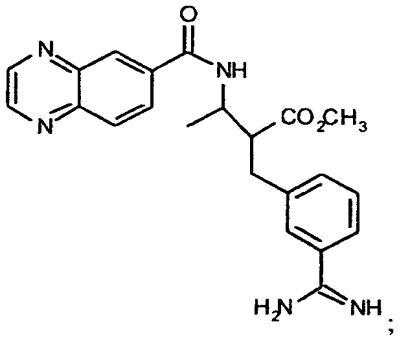

;


;

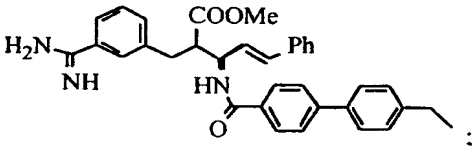

;

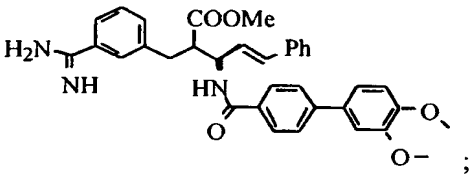


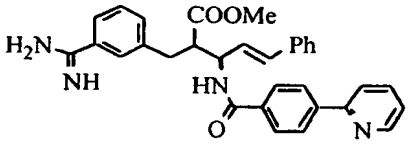


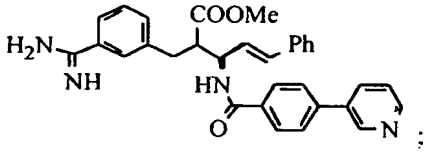


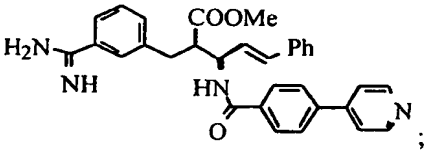
5



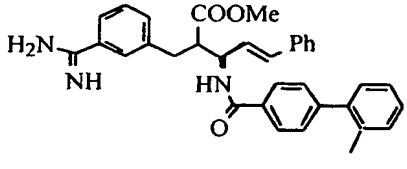


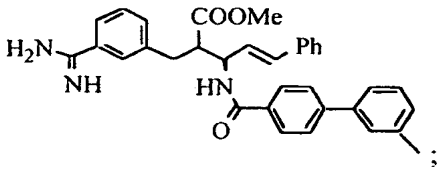


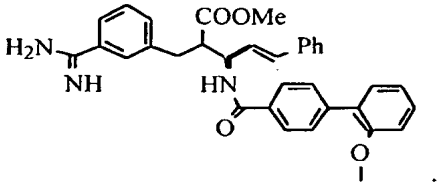


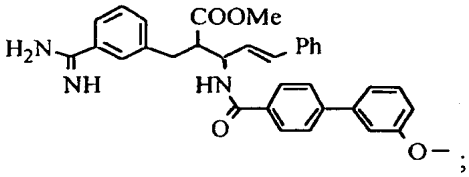


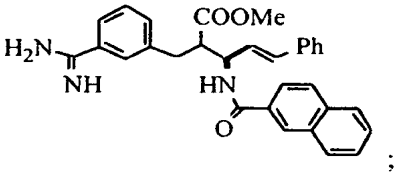
10

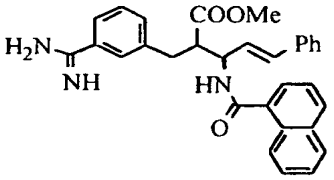


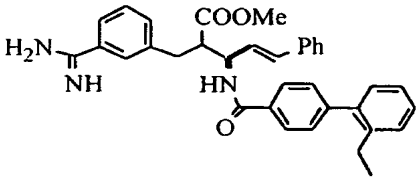

;

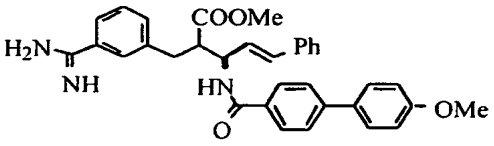

;

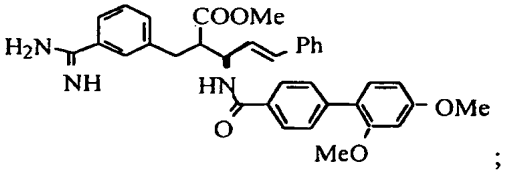

;

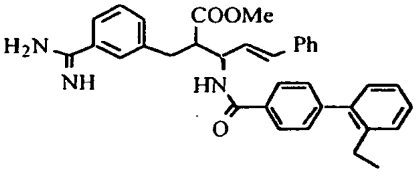

;

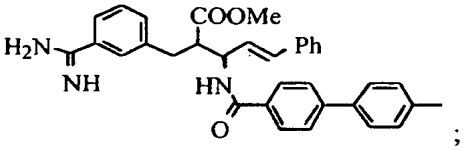

;

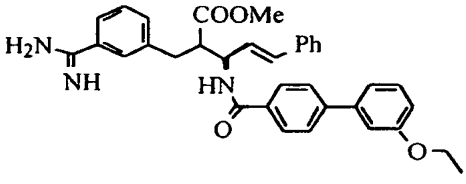

;

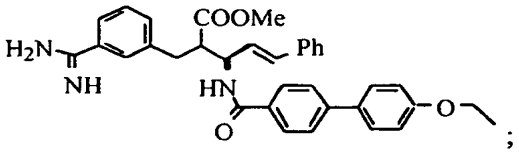

;

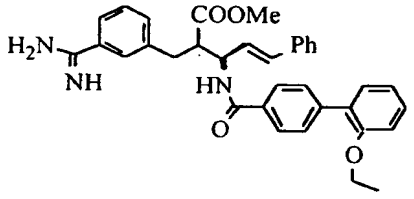
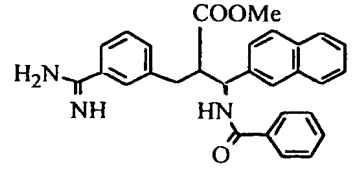

;

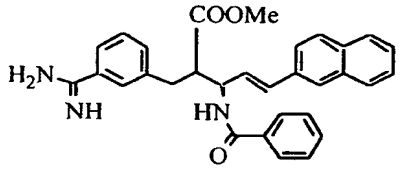
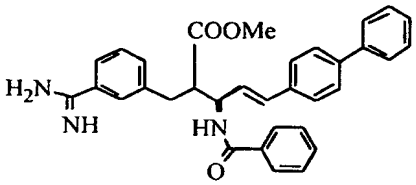

;

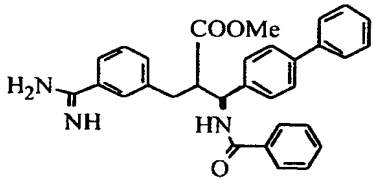
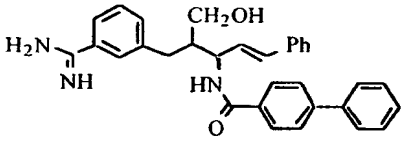

;

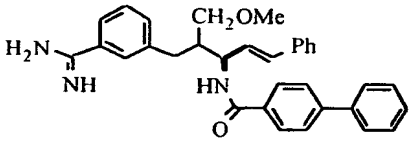
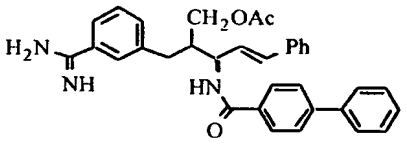

;

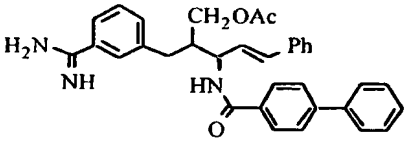
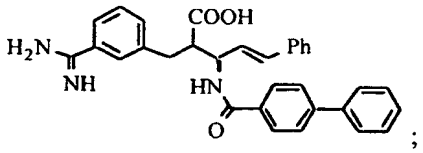

;

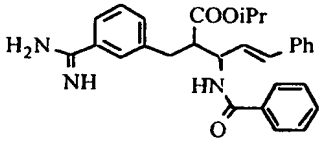
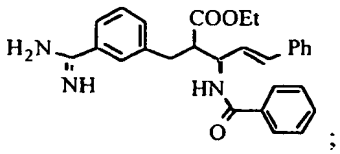

;

;

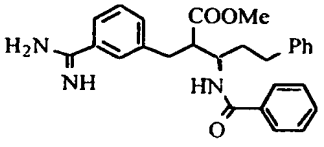
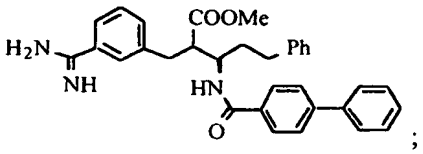

;

;

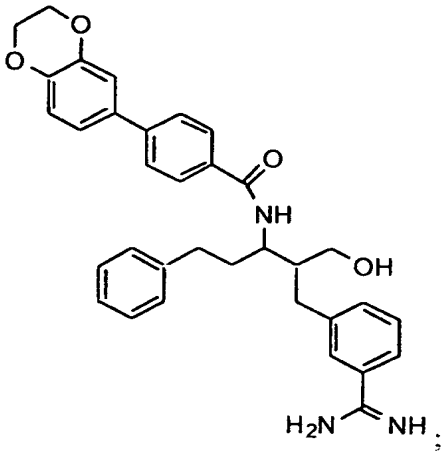

;

;

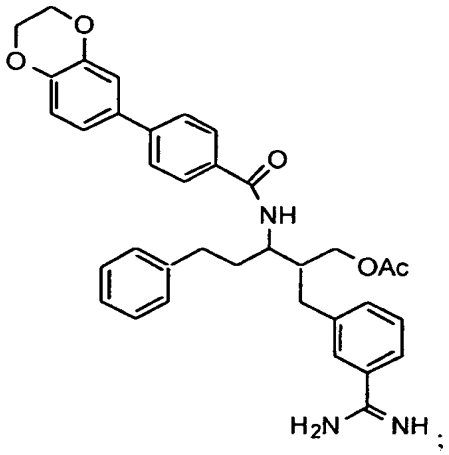

;

;

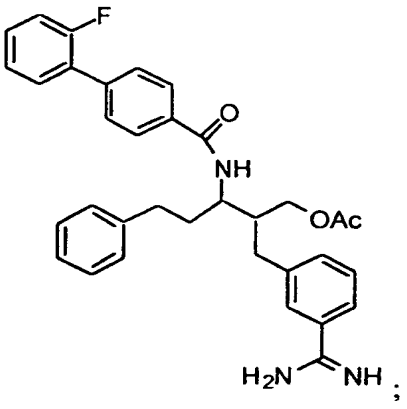

;

;

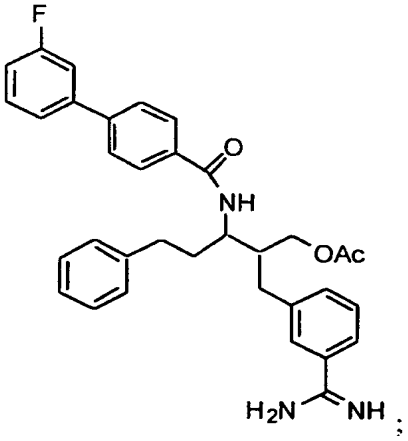

;

;

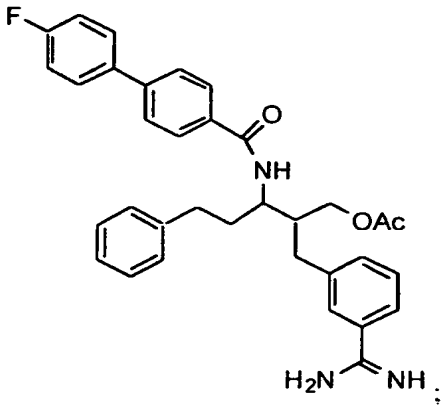

;

;

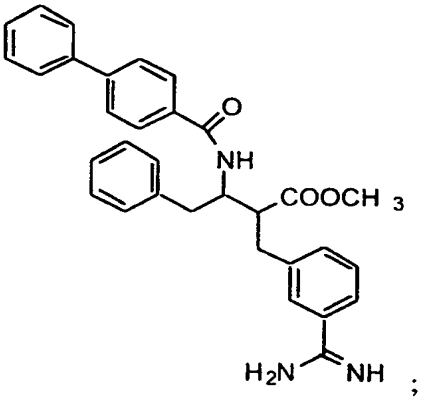




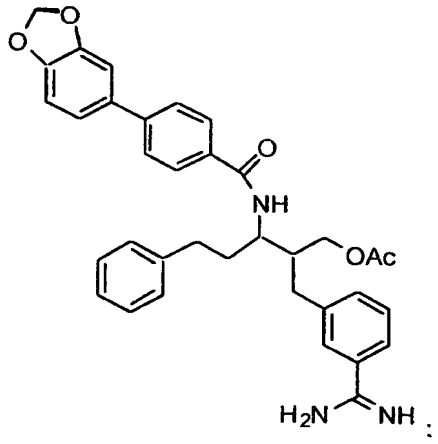


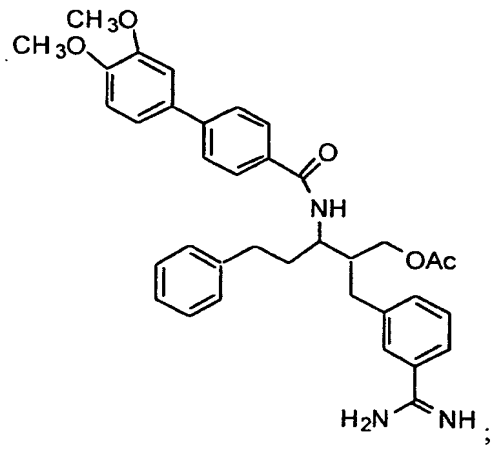


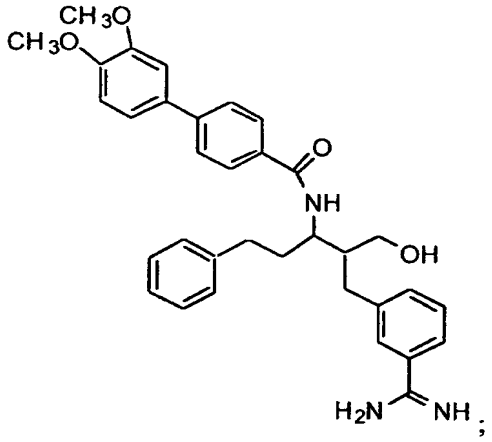


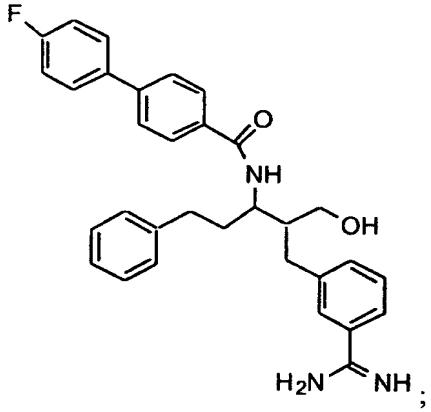


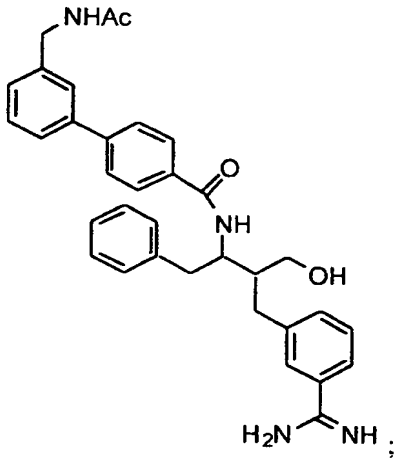
5

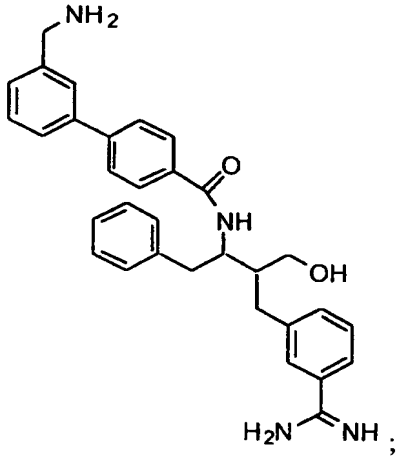




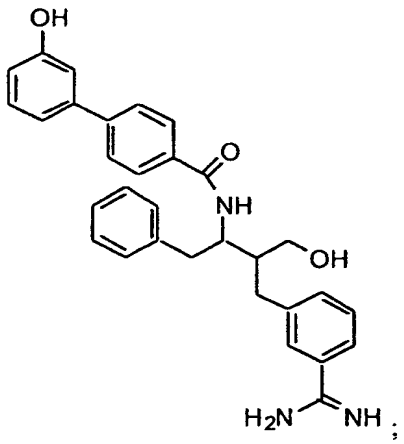


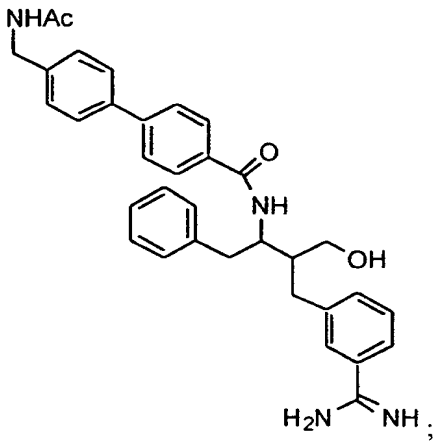


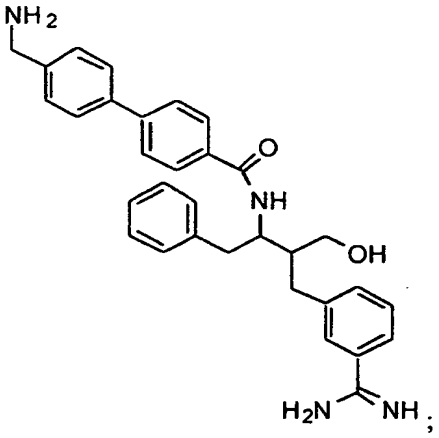


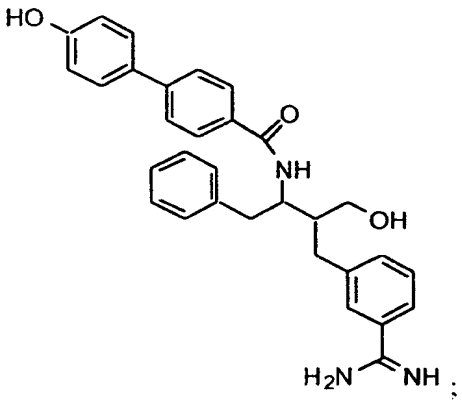


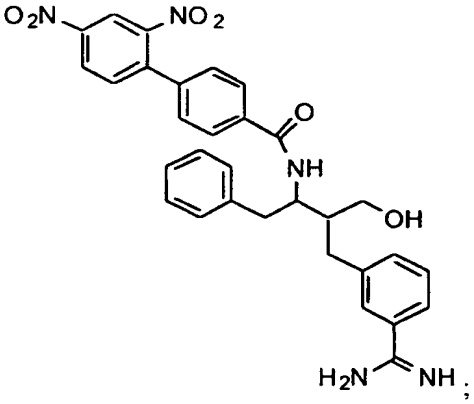
5

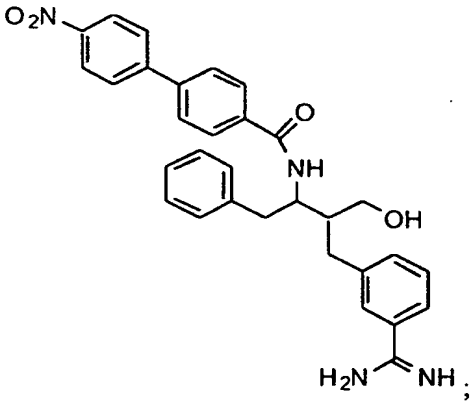


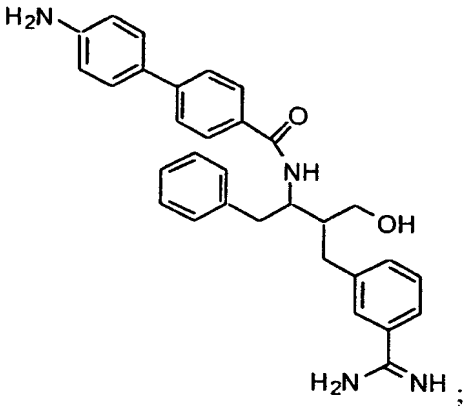


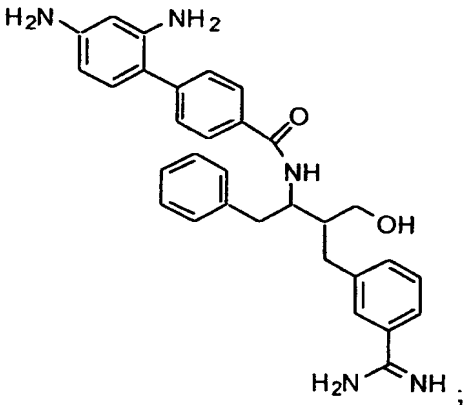


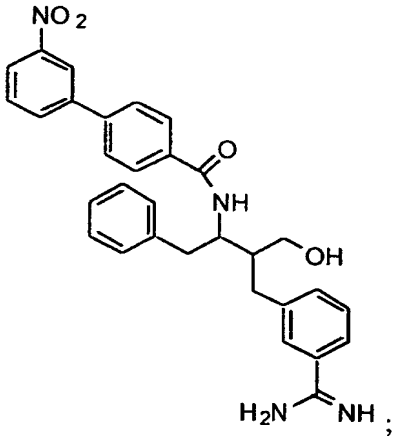


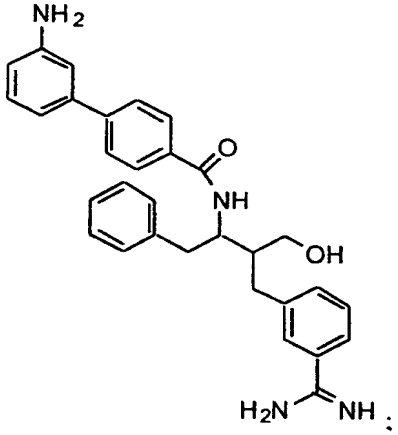


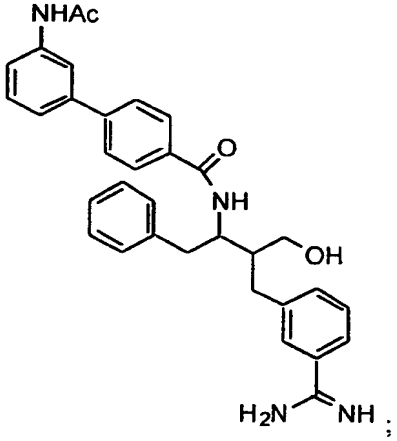


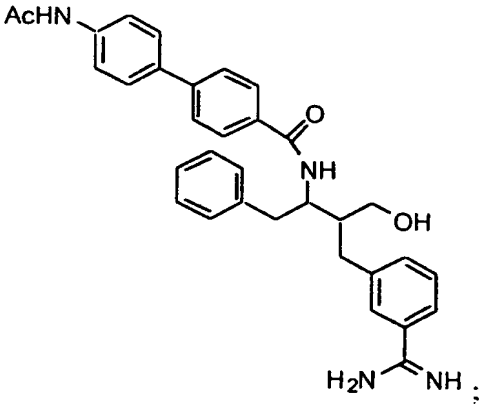




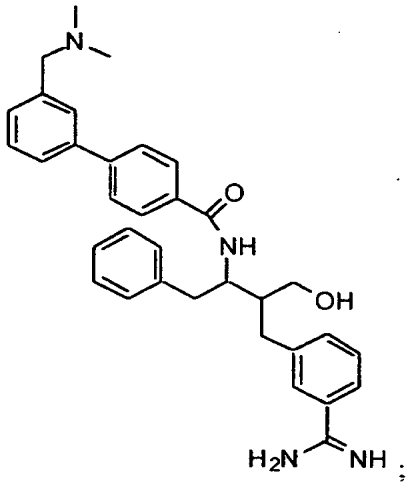


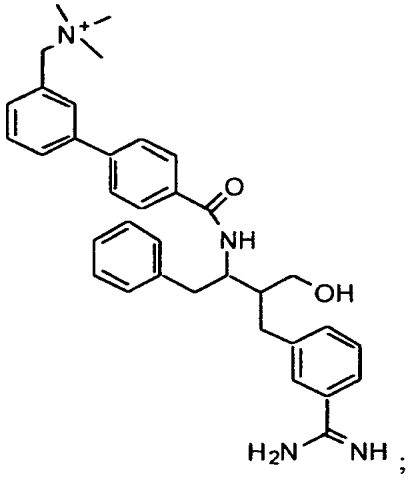


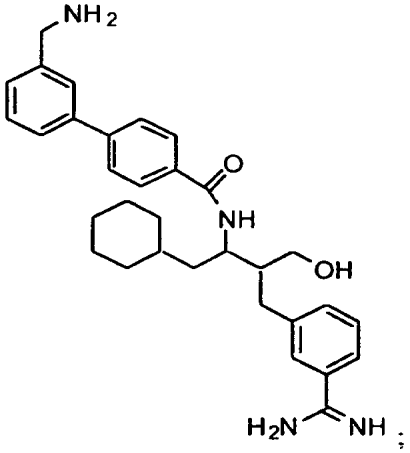


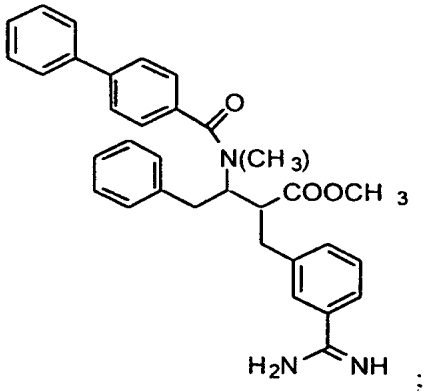


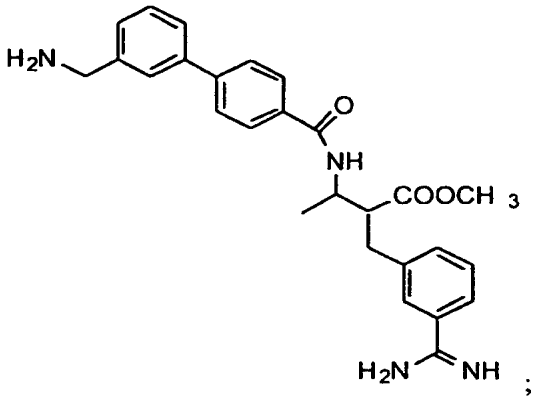
5

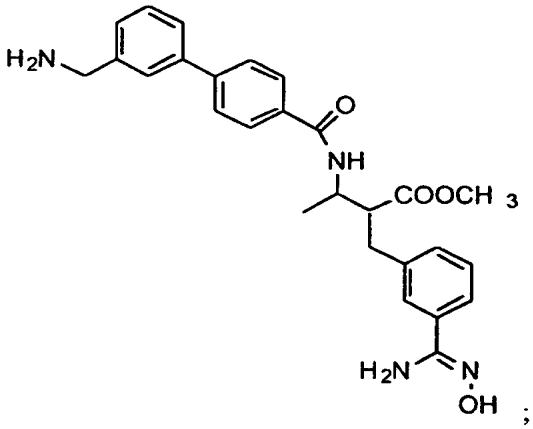

N
O
NH
OH
H2N
NH
;

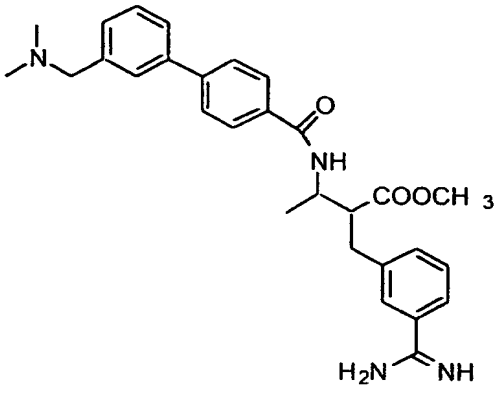

N+
O
NH
OH
H2N
NH
;

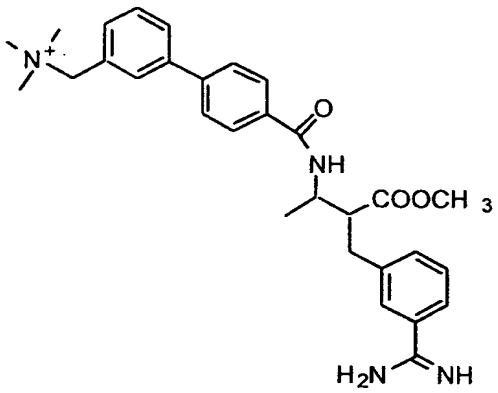

NH2
O
NH
OH
H2N
NH
;

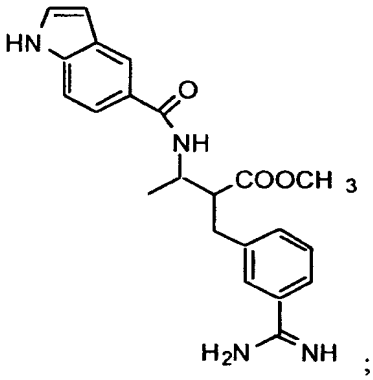

O
N(CH3)
COOCH3
H2N
NH
;

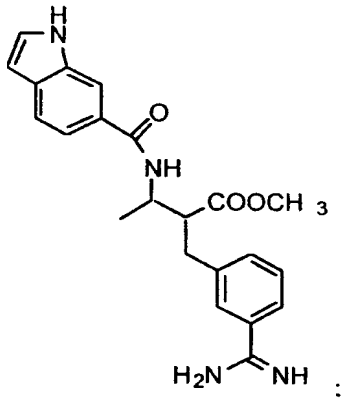

H2N
O
NH
COOCH3
H2N
NH
;

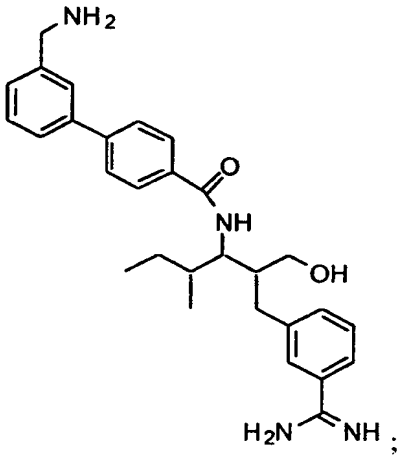

H2N
O
NH
COOCH3
H2N
N
OH
;

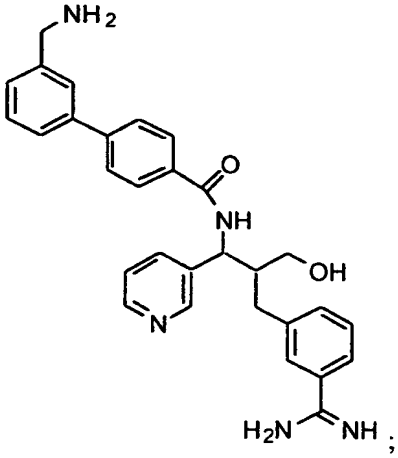

N
O
NH
COOCH 3
H2N
NH
;

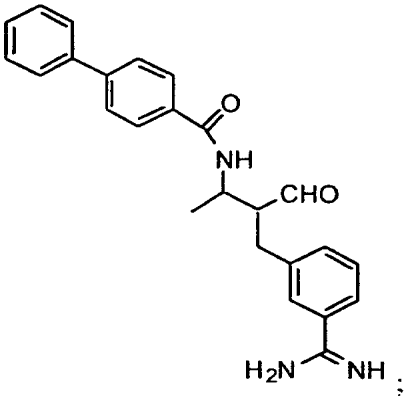

N+
O
NH
COOCH 3
H2N
NH
;

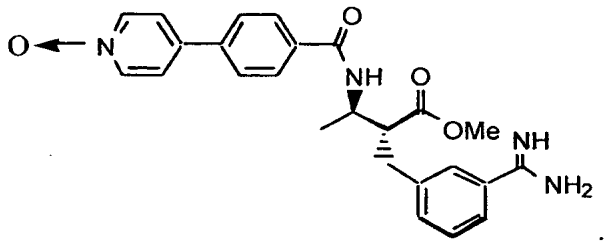

HN
O
NH
COOCH 3
H2N
NH
;

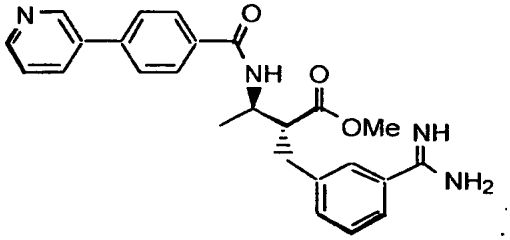

H
N
O
NH
COOCH 3
H2N
NH
:

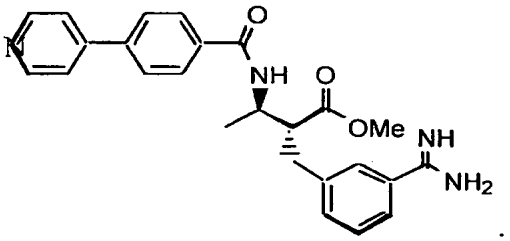

NH2
O
NH
OH
H2N
NH
;

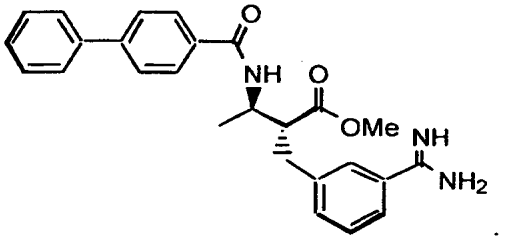

NH2
O
NH
OH
N
H2N
NH
;

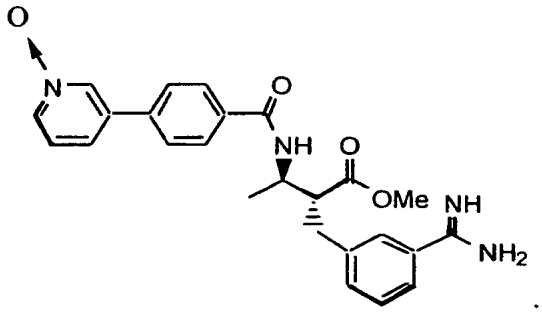

O
NH
CHO
H2N
NH
;

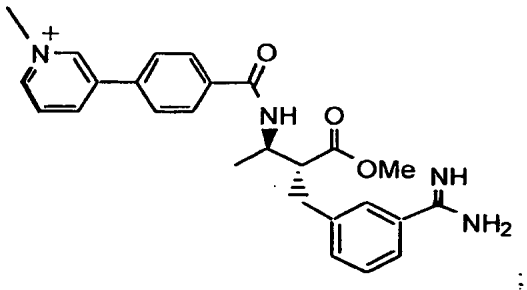

O
N
O
NH
O
OMe
NH
NH2
;

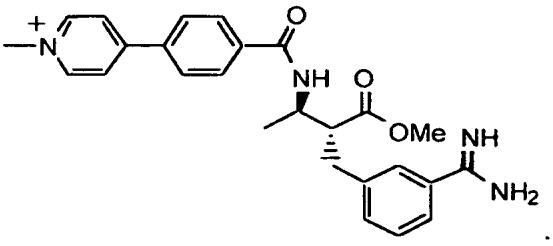

N
O
NH
O
OMe
NH
NH2
;

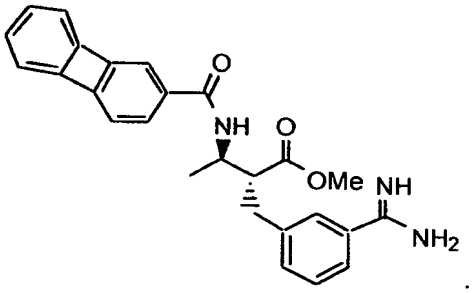

N
O
NH
O
OMe
NH
NH2
:

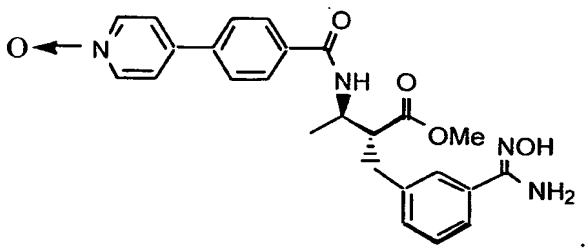

O
NH
O
OMe
NH
NH2
;

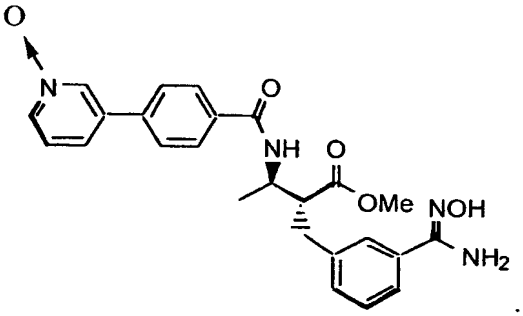

O
N
O
NH
O
OMe
NH
NH2
;

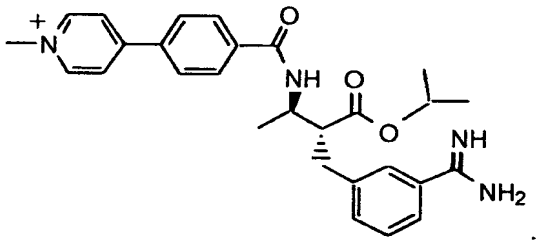

N
+
O
NH
O
OMe
NH
NH2
;

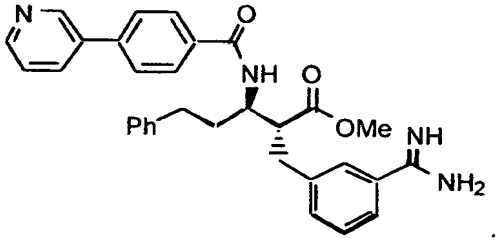

+
N
O
NH
O
OMe
NH
NH2
;

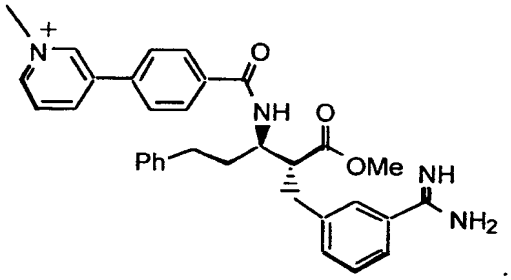

;

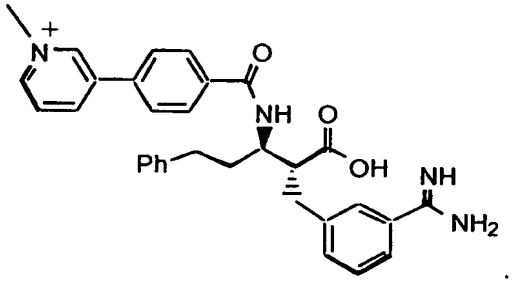

;

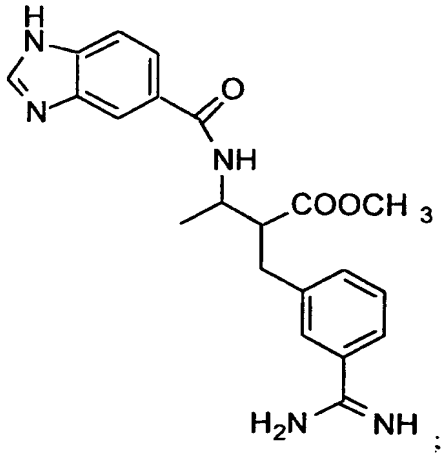

;

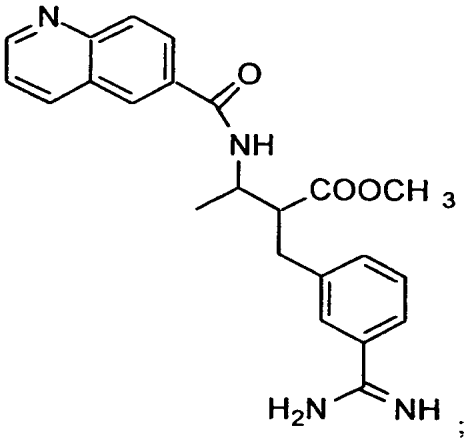

;

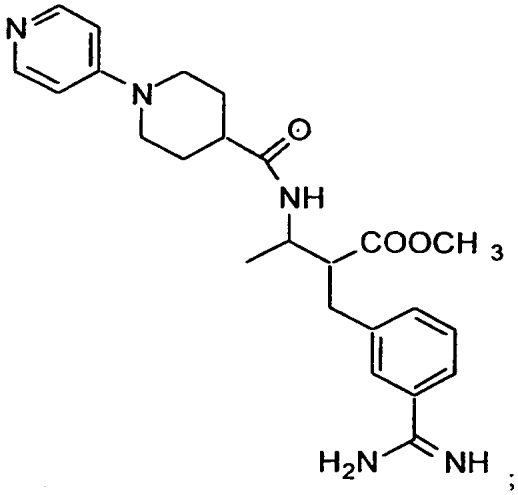

;

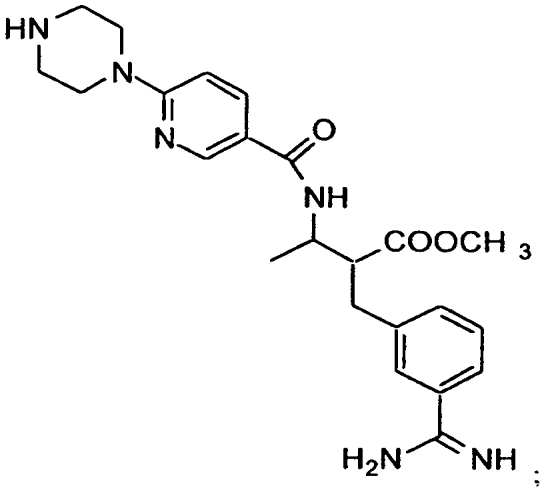

;

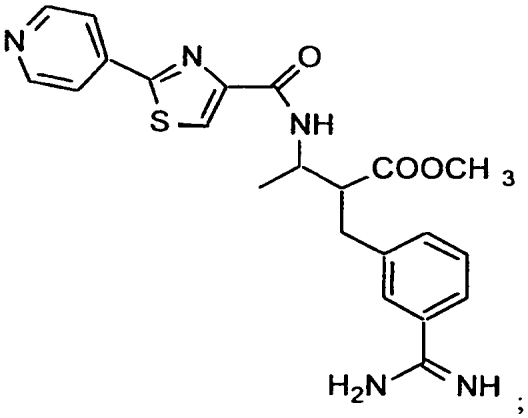

;

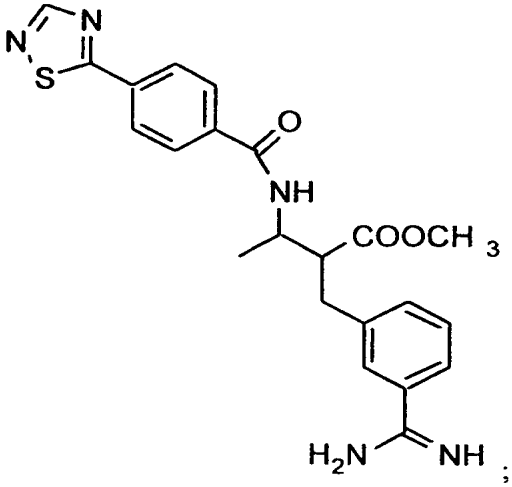

;

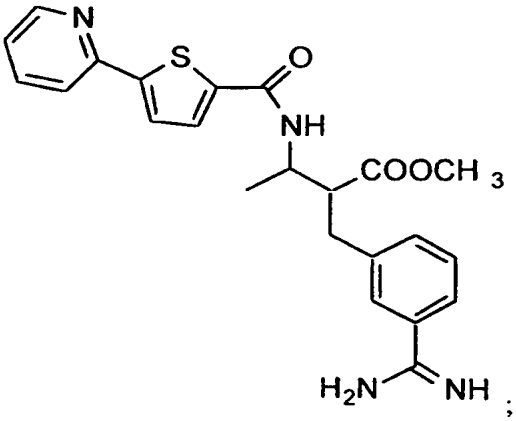


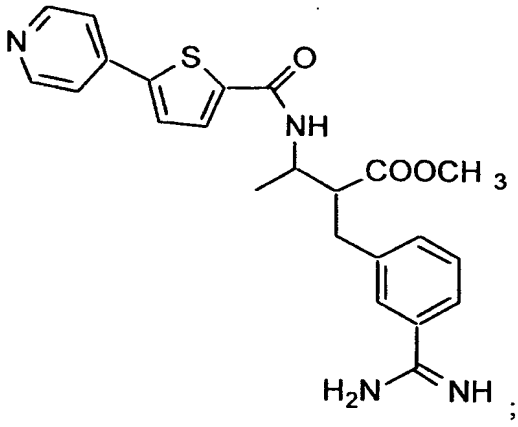


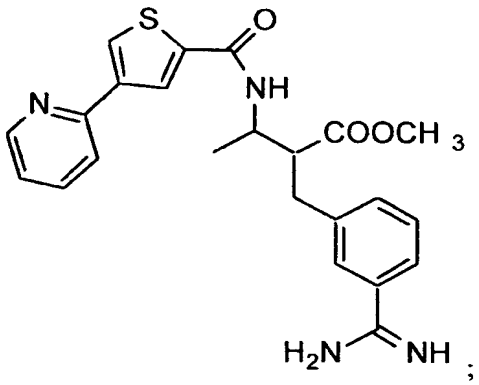


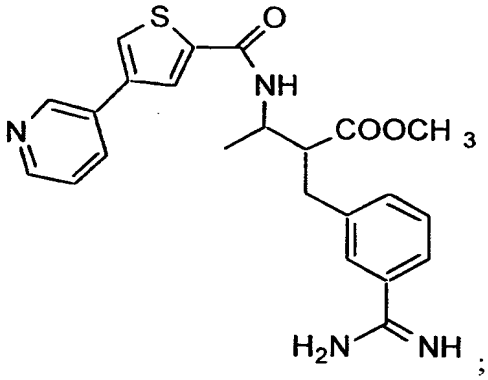


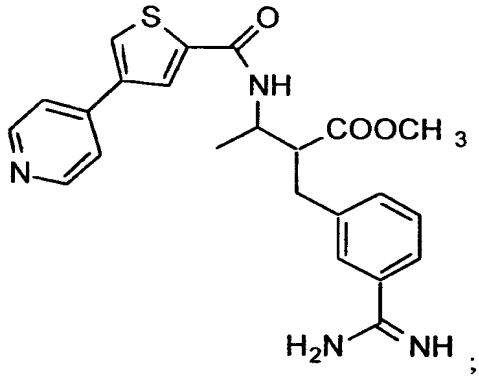




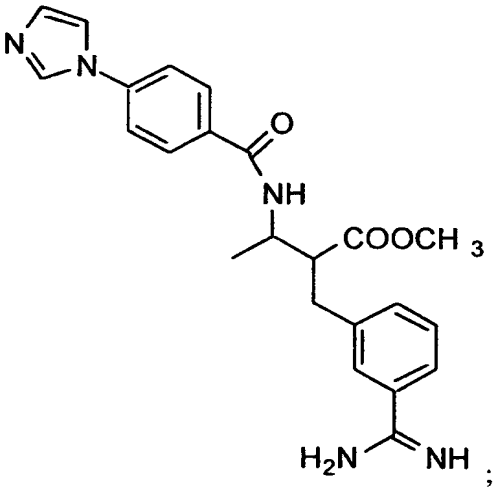


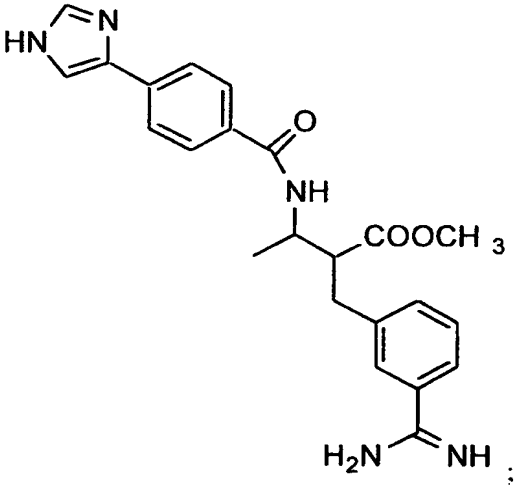


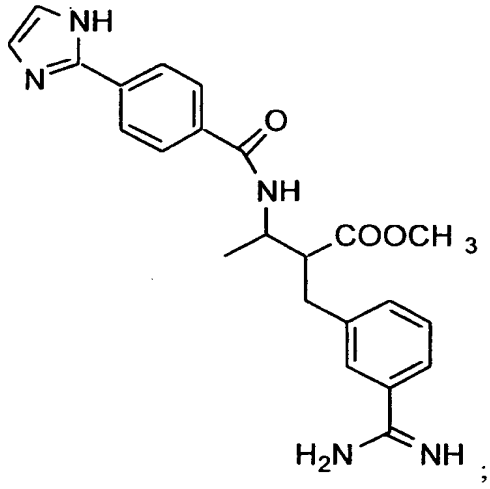




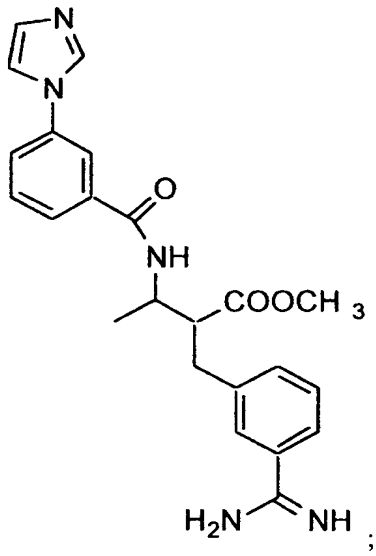
5



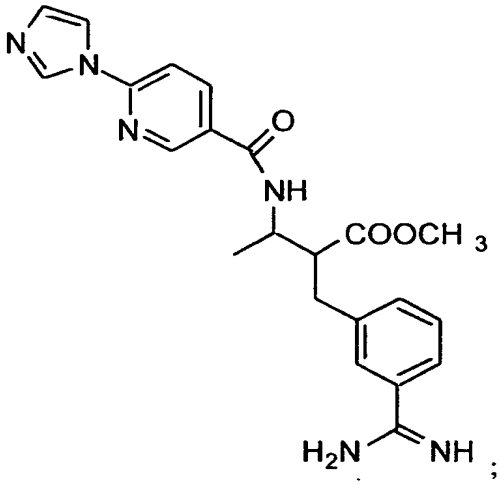




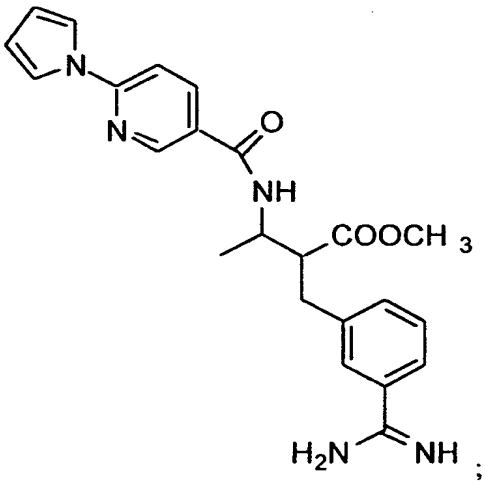
;



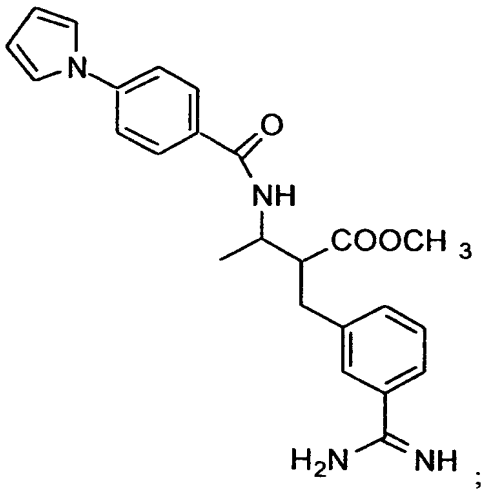
;

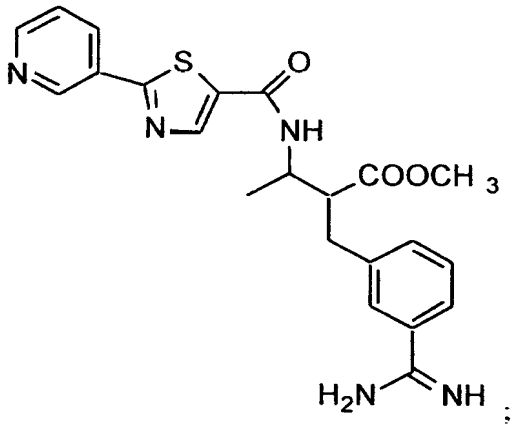


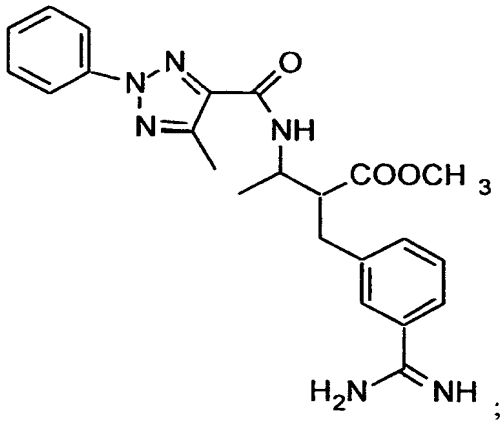
;

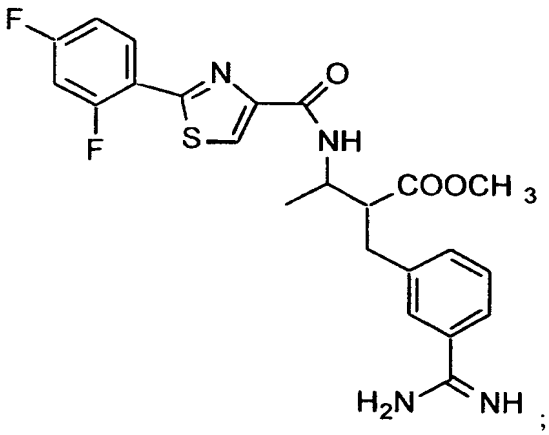


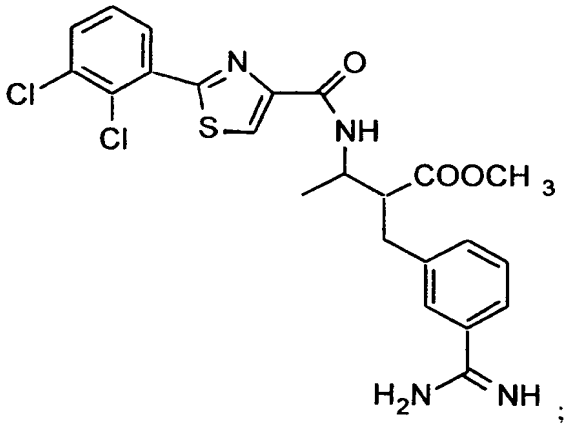
;

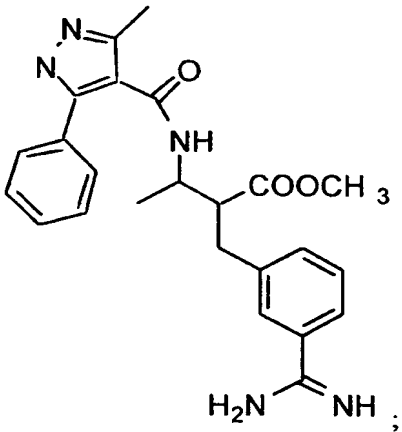


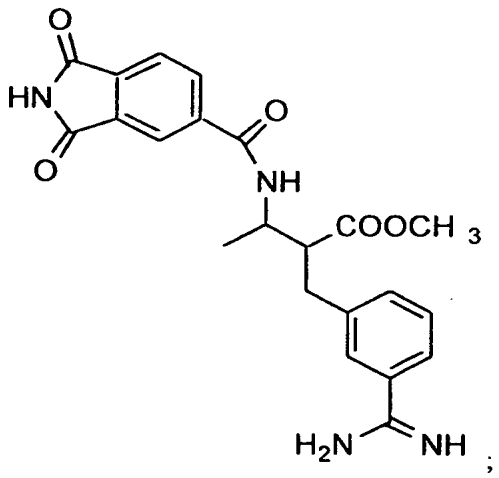


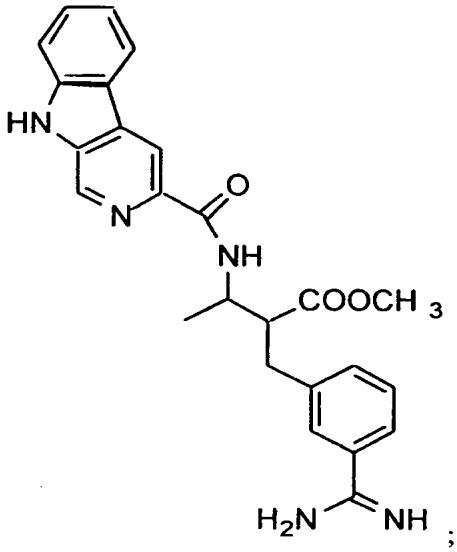


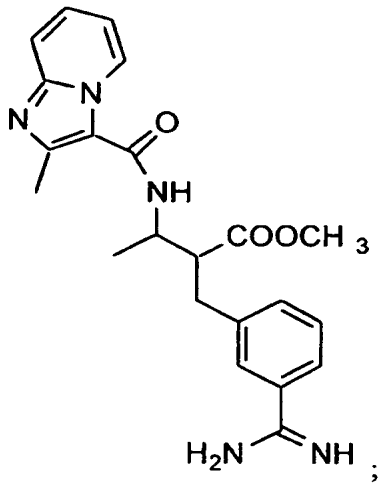


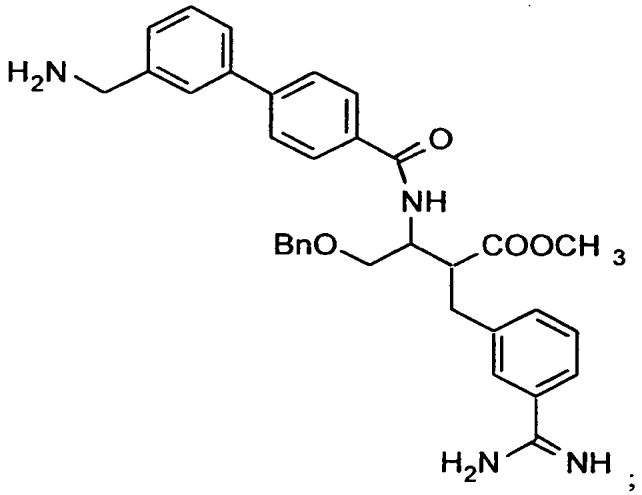


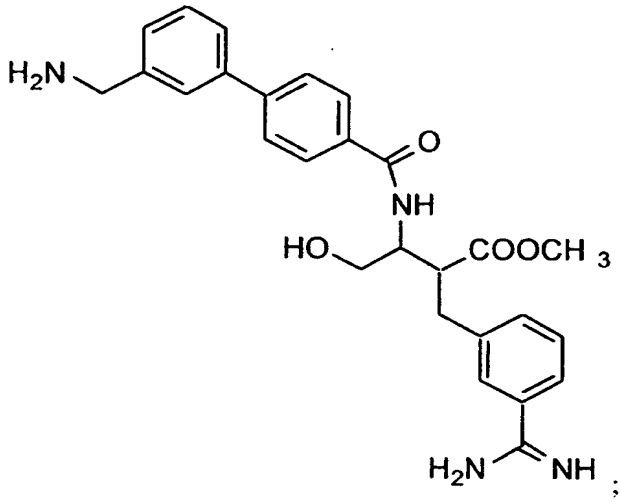


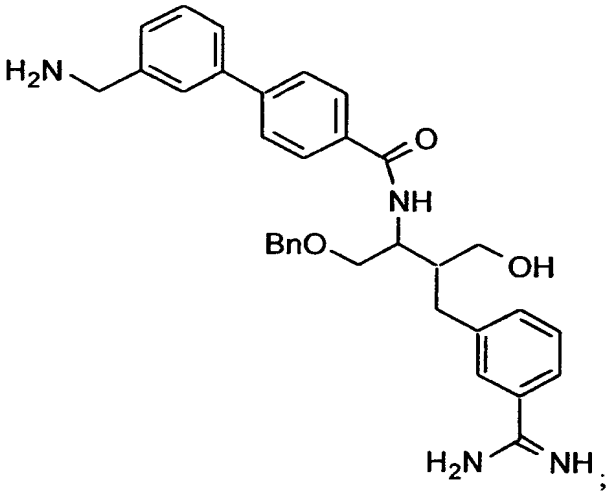


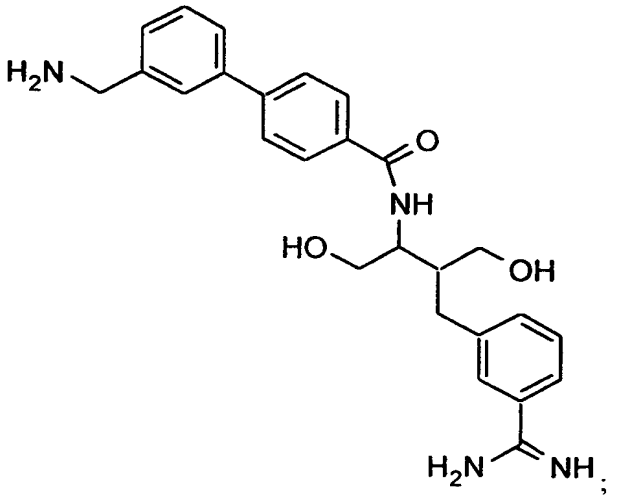




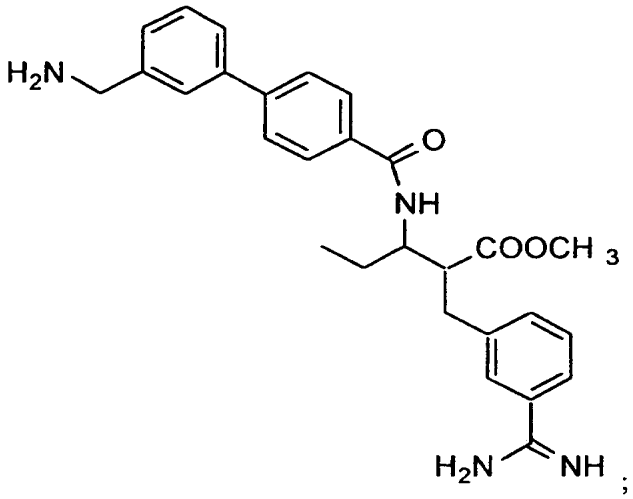


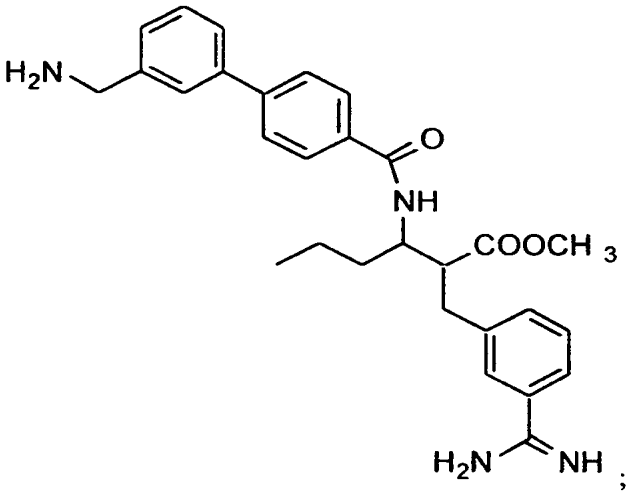




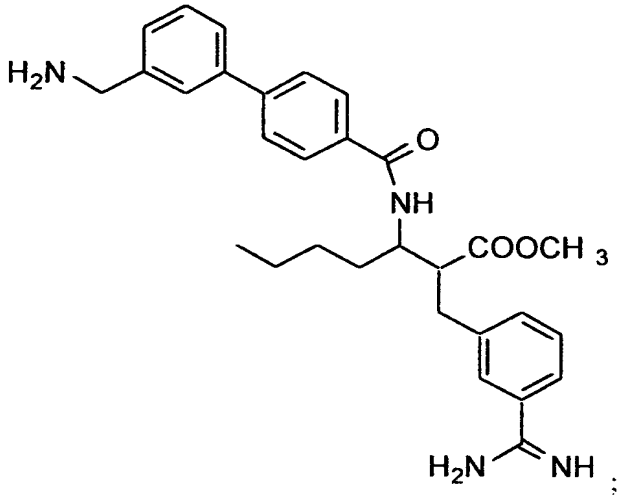


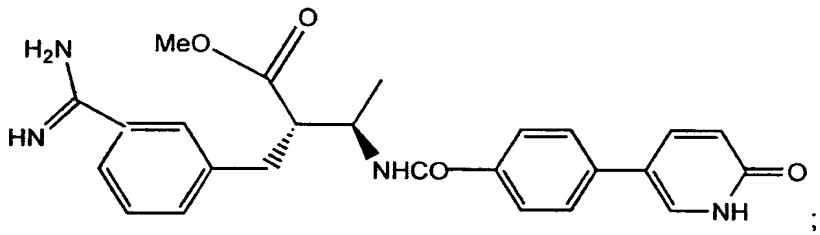
5

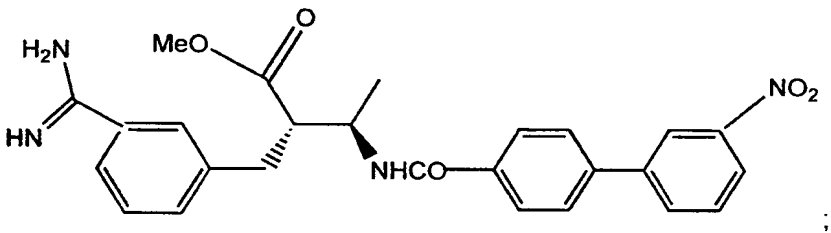




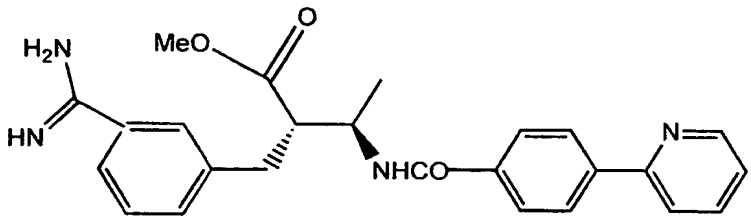
5

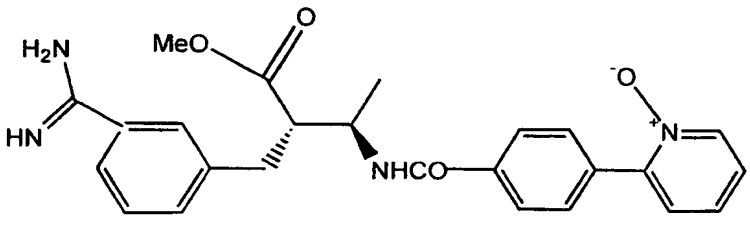


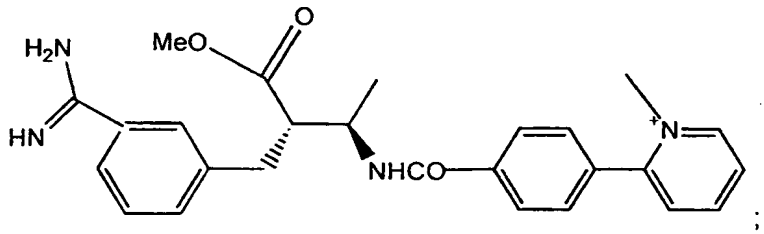




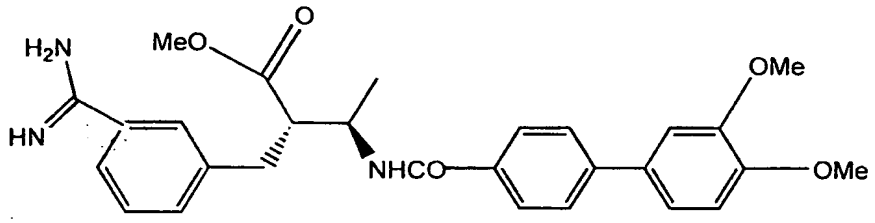
5



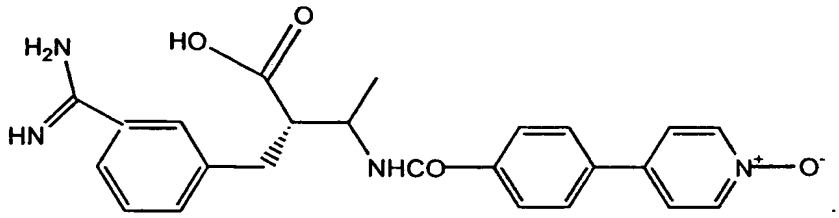




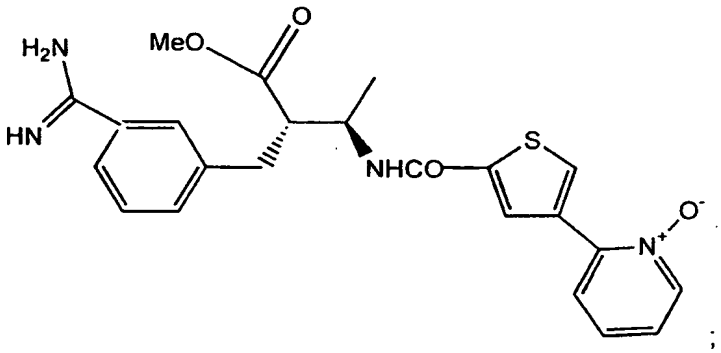
;



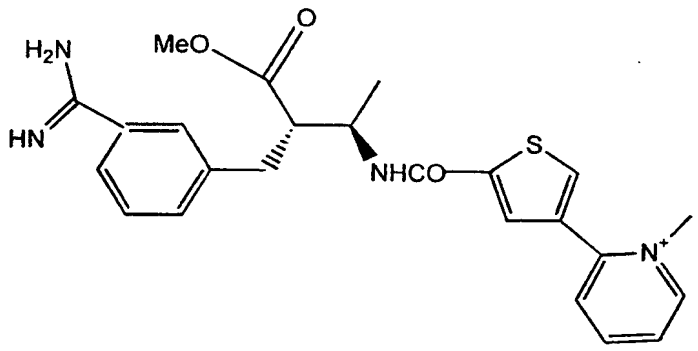
;



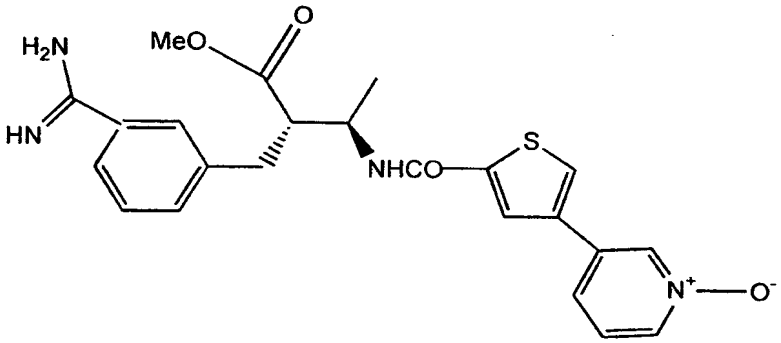
;



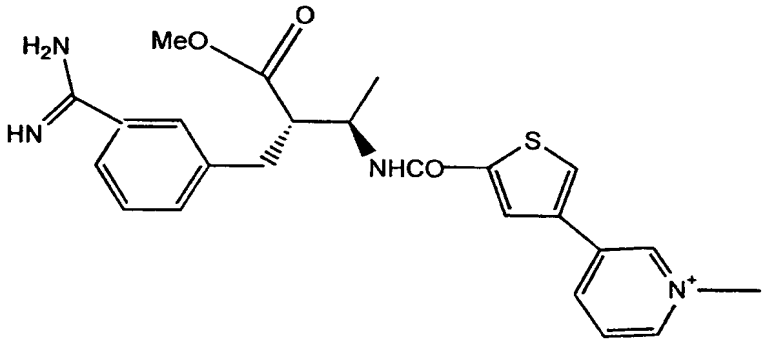
;



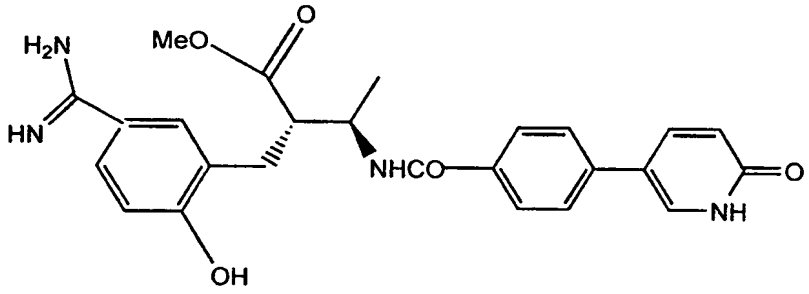
;



;



;



;

(Z)-N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)allyl]-4-pyridin-3-ylbenzamide;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-pyridin-3-yl)-benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(1-oxy-pyridin-4-yl)-benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(6-oxo-1,6-dihydropyridin-3-yl-benzamide trifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(pyridazin-4-yl)benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-7-chlorobenzothiophene-2-carboxamide trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide trifluoroacetate;

(E)-Biphenyl-4-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-pyridin-3-yl-benzamide ditrifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-pyridin-4-yl-benzamide ditrifluoroacetate;

(E)-Biphenyl-3,4'-dicarboxylic acid 3-amide 4'-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide} trifluoroacetate;

(E)-4-tert-Butyl-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-benzamide trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(3H-imidazol-4-yl)-benzamide ditrifluoroacetate;

(E)-Biphenyl-4,4'-dicarboxylic acid 4'-amide 4-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide} trifluoroacetate;

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(1H-imidazol-2-yl)-benzamide ditrifluoroacetate;

(E)-3-Oxo-2,3-dihydro-thieno[3,2-c]pyridazine-6-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide trifluoroacetate;

(E)-5-Pyridin-2-yl-thiophene-2-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide ditrifluoroacetate;

Biphenyl-4-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-propyl]-amide trifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(6-methoxy-pyridin-3-yl)-benzamide trifluoroacetate;

Biphenyl-3,4'-dicarboxylic acid 3-amide 4'-{[3-(5-carbamimidoyl-2-hydroxy-phenyl)- propyl]-amide} trifluoroacetate;

4-tert-Butyl-N-[3-(5-carbamimidoyl-2-hydroxy-phenyl)-propyl]-benzamide trifluoroacetate;

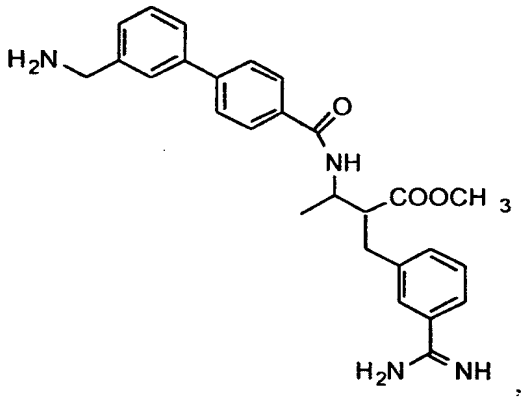
[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(3H-imidazol-4-yl)-benzamide ditrifluoroacetate;

N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-(1H-imidazol-2-yl)-benzamide ditrifluoroacetate;

5-Pyridin-2-yl-thiophene-2-carboxylic acid [3-(5-carbamimidoyl-2-hydroxy-phenyl)-allyl]-amide ditrifluoroacetate; or

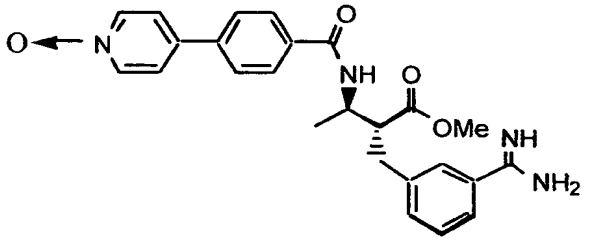
N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-propyl]-4-piperidin-4-yl-benzamide ditrifluoroacetate, or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

39. A compound according to claim 1 which is



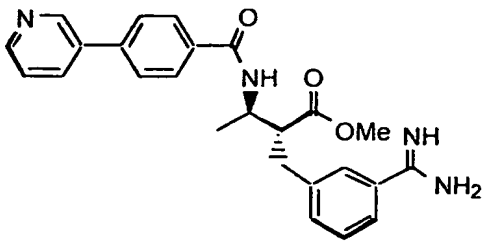
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

40. A compound according to claim 1 which is



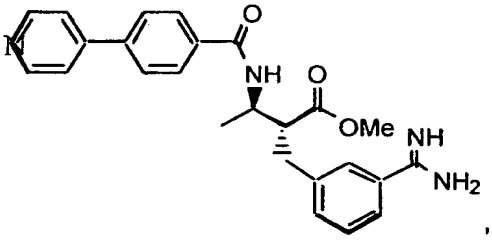
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

41. A compound according to claim 1 which is



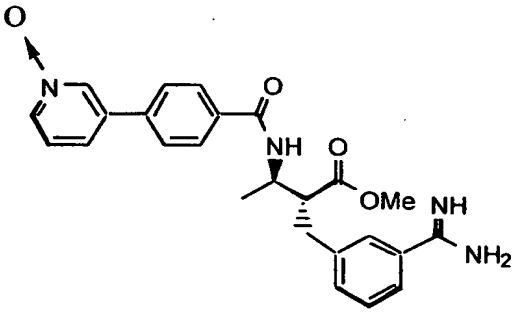
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

42. A compound according to claim 1 which is



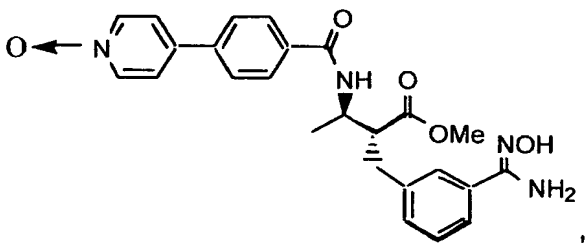
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

43. A compound according to claim 1 which is



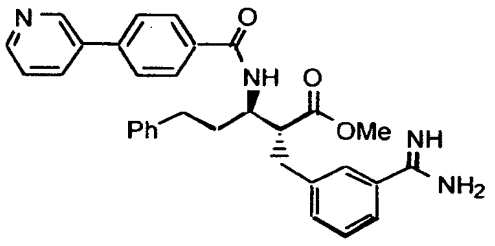
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

44. A compound according to claim 1 which is



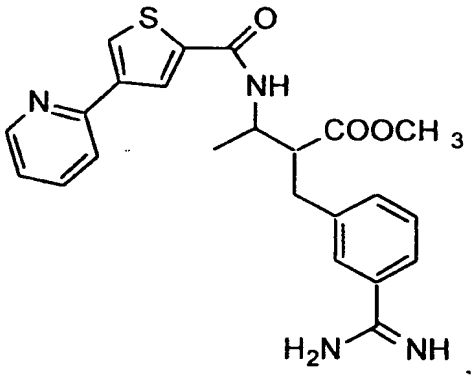
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

45. A compound according to claim 1 which is



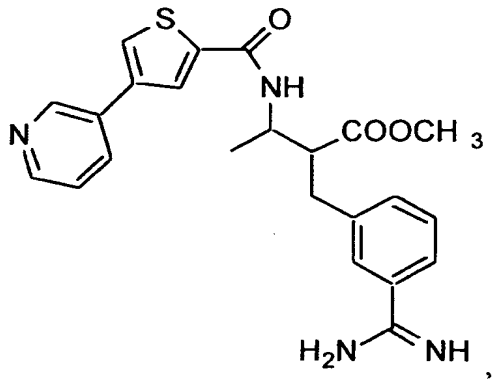
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

46. A compound according to claim 1 which is



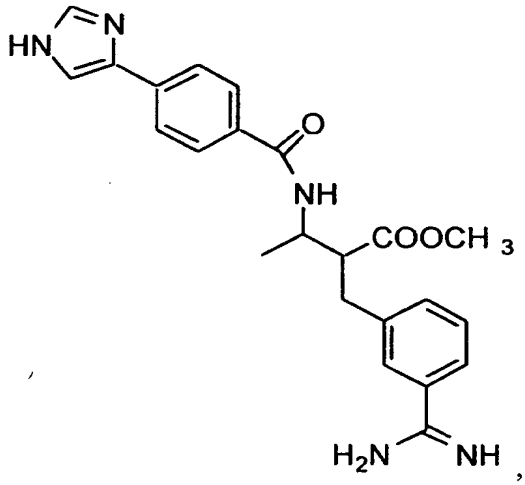
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

47. A compound according to claim 1 which is



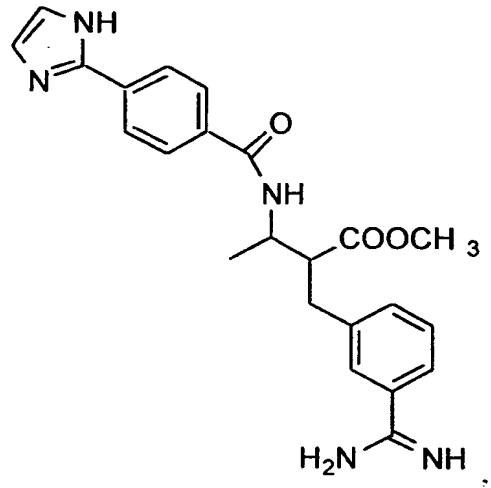
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

48. A compound according to claim 1 which is



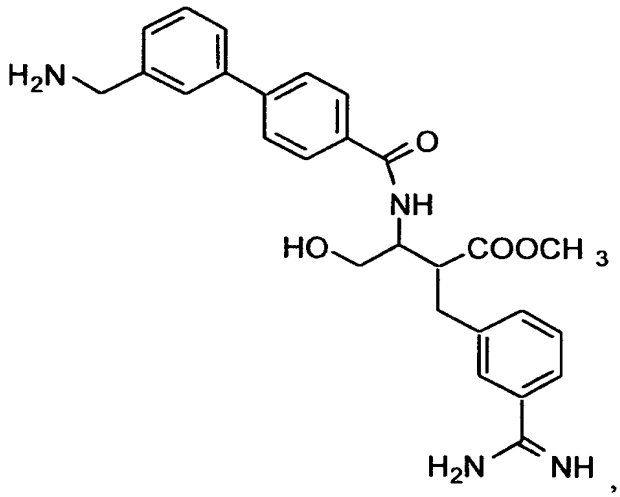
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

49. A compound according to claim 1 which is



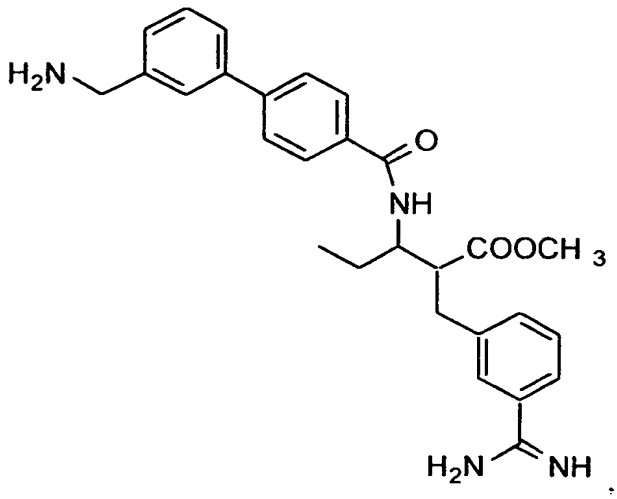
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

50. A compound according to claim 1 which is



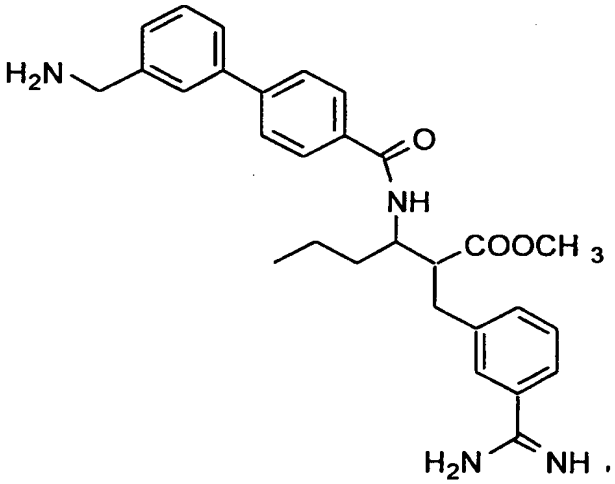
or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

51. A compound according to claim 1 which is



or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

52. A compound according to claim 1 which is



or a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

53. A compound according to claim 1 which is

2-(R)-(3-Carbamimidoyl-benzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester trifluoroacetate, or

a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

54. A compound according to claim 1 which is

2(R)-(3-Carbamimidoyl-6-hydroxybenzyl)-3(R)-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzoylamino]-butyric acid methyl ester, or

a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

55. A compound according to claim 1 which is

N-[3-(5-Carbamimidoyl-2-hydroxyphenyl)-propyl]-4-(6-oxo-1,6-dihydropyridin-3-yl-benzamide trifluoroacetate, or

a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

56. A compound according to claim 1 which is

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzamide trifluoroacetate, or

a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

57. A compound according to claim 1 which is

(E)-N-[3-(5-Carbamimidoyl-2-hydroxy-phenyl)-allyl]-4-(1-oxy-pyridin-4-yl)-benzamide ditrifluoroacetate, or

a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

58. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

59. A method for treating a patient suffering from a disease state capable of being modulated by inhibiting production of Factor Xa comprising administering to said patient a pharmaceutically effective amount of the compound according to claim 1.

60. A method of inhibiting factor Xa comprising contacting a Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

61. A method of inhibiting the formation of thrombin comprising contacting Factor Xa inhibitory amount of a compound according to claim 1 with a composition containing Factor Xa.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13550

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07C 257/18; C07D 213/58; A61K 31/215, 44
US CL : 560/35; 546/332; 514/357, 539

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 560/35; 546/332; 514/357, 539

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,424,334 A (ABOOD et al) 13 June 1995 examples 12, 14 16	1-61

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 SEPTEMBER 1998	Date of mailing of the international search report 26 OCT 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT GERSTL Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*